

REVIEW ARTICLE

Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group

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Abstract

Angioedema owing to hereditary deficiency of C1 inhibitor (HAE) is a rare, life-threatening, disabling disease. In the last 2 years, the results of well-designed and controlled trials with existing and new therapies for this condition have been published, and new treatments reached the market. Current guidelines for the treatment for HAE were released before the new trials and before the new treatments became available and were essentially based on observational studies and expert opinion. To provide evidence-based HAE treatment guidelines supported by the new studies, a conference was held in Gargnano del Garda, Italy, from September 26 to 29, 2010. The meeting hosted 58 experienced HAE expert physicians, representatives of pharmaceutical companies and representatives of HAE patients' associations. Here, we report the topics discussed during the meeting and evidence-based consensus about management approaches for HAE in adult/adolescent patients.

Hereditary angioedema with C1 inhibitor (C1-INH) deficiency (HAE) is a rare disease with an estimated frequency of 1 : 50 000 in the general population without major racial or gender differences (1). HAE is clinically manifested by recurrent episodes of localized subcutaneous or submucosal edema lasting for 2–5 days. The most commonly involved organs include the skin, upper respiratory tract, oropharynx, and gastrointestinal tract. The disease is disabling and can be lethal (2, 3). Effective management of HAE is targeted to either preventing or treating attacks. Drugs for both approaches have been available since the late 1970s, but not uniformly registered. Owing to the paucity of controlled studies, treatment modalities had been mostly empiric, and

consensus guidelines were primarily based on limited case series, observational studies, and expert opinions, until now (4–6).

Treatment for HAE has been revolutionized in the last 10 years by three new drugs developed for the treatment for acute attacks. To obtain marketing authorization, the three new drugs and two plasma-derived C1-INHs (pdC1-INH) already available in some countries underwent controlled trials (7–12). Recent publication of these trials prompted a re-evaluation of existing guidelines to move from expert opinions to evidence-based recommendation.

With this in mind, a conference was held in Gargnano del Garda, Italy, from September 26 to 29, 2010. The meeting

hosted 58 experienced HAE expert physicians from 17 countries (listed as Hereditary Angioedema International Working Group, HAWK), 22 representatives of the five pharmaceutical companies producing drugs for HAE (CSL Behring, Marburg, Germany; Dyax, Cambridge, MA, USA; Pharming, Leiden, The Netherlands; Shire, Jersey, JE, USA and ViroPharma, Exton, PA, USA), and nine representatives of HAE patients' associations. Here, we report the data reviewed during the meeting and the consensus document eventually approved by the 58 HAE expert physicians. Other issues of HAE treatment, such as pediatric patients' approach, pregnancy, and short-term prophylaxis, that have never been tested in a controlled clinical trials were not covered by the meeting and are not mentioned here; they can be found in existing consensus publications (3–6).

Validated instruments for assessing severity of acute HAE attacks

This part is available as Addendum, Supporting Information.

Long-term prophylaxis (LTP) of attacks

General considerations

This treatment approach is aimed to reduce the burden of the disease by preventing/attenuating angioedema recurrences. It is given, by definition, to patients when they are symptom free, and therefore, it is administered continuously and potentially for life. Based on clinical experience, it has been suggested to consider an LTP approach when patients, despite optimized on-demand treatment of angioedema attacks, continue experiencing more than 12 moderate-to-severe attacks per year or more than 24 days per year affected by HAE (3).

Crucial to the decision of starting a patient on LTP is an expectation that benefits will outweigh expected side-effects. Assessment of disease severity, treatment efficacy and safety profile are essential elements for consideration.

Three classes of drugs, attenuated androgens, antifibrinolytic agents and plasma-derived C1-INH concentrates, underwent controlled clinical trials against placebo, and these trials proved their efficacy for LTP in HAE (7, 13–17).

Attenuated androgens

In a double-blind, randomized crossover study on nine HAE patients, of 47 placebo courses, 44 ended with attacks, but during 46 danazol (600 mg/day) courses, only one attack occurred (2.2% vs 93.6%, $P < 0.001$). C1-INH levels increased three to four times, and levels of the fourth component of complement (C4) increased 15 times in danazol-treated patients (14). In a similar study, methyltestosterone (10 mg/day) reduced HAE attack frequency from 19 attacks/11.8 month to 4 attacks/46 months (16). Efficacy of danazol and other androgen derivatives was further confirmed in observational studies using lower doses to reduce side-effects (18–22).

Adverse effects

It has been estimated that around one-third of recognized HAE patients have been exposed to LTP with androgen derivatives in the last 35 years. This large experience allows the identification of side-effects and facilitates the definition of risk–benefit profile (23). Androgen-related side-effects are dose dependent and commonly related to residual hormonal activity. Bork et al. (21) described weight gain, virilization, menstrual irregularities, headache, depression, and/or liver adenomas in 93 of 118 patients treated with androgen derivatives for periods ranging between 2 months and 30 years. Because of these effects, 30 patients (25.4%) discontinued therapy. Cicardi et al. (24) compared 36 HAE patients on androgen derivatives for a median of 125 months with 33 HAE patients, who never received such treatment. Arterial hypertension was present in 25% of patients in the treated group but only in 3% of the controls. Other side-effects of chronic androgen use include liver enzyme elevation, liver tumors, and dyslipidemia. Hepatocellular adenoma, carcinoma, or focal nodular hyperplasia related to danazol treatment have been reported in seven HAE patients (25–29). Adverse effects on lipid profile, but no increase in carotid intima-media thickness or prevalence of vascular disease HDL cholesterol, have been related to LTP with androgen derivatives in HAE patients (30–32).

Dosage

Observational studies demonstrated that the efficacy of LTP with androgen derivatives in HAE is dose dependent, but clinically effective doses do not require a significant increase in C1-INH plasma levels (33). Each individual treatment needs to be empirically titrated to the minimal effective dose (34). Retrospective analysis of large case lists suggests that recommended doses with acceptable long-term adverse effects are danazol ≤ 200 mg/day and stanozolol ≤ 2 mg/day (21, 24, 35).

Contraindications

Owing to residual androgenic hormonal activity, androgen derivatives are not recommended for women in pregnancy/lactation or children until after growth is complete.

Monitoring

Regular follow-up visit every 6 months is recommended. Liver enzymes, lipid profile, complete blood cell count, alpha-feto-protein, and urinalysis should be performed. Abdominal ultrasound yearly is advisable for early diagnosis of liver tumors (26).

Antifibrinolytics

This part is available as Addendum.

Plasma-derived C1-INH concentrates

Plasma-derived C1-INH concentrate, given intravenously, has been used for LTP since 1989 (36). In a double-blind, placebo-controlled crossover study (six patients in two 17-day

periods), a C1-INH preparation no more on the market at 25 U/kg every 3 days reduced HAE disease activity by 60% (17). In a more recent study (22 patients in two 12-week periods), C1-INH (Cinryze®) at 1000 U every 3–4 days reduced HAE attacks from 12.73 to 6.26 ($P < 0.001$), which is a 50% reduction in attacks. In addition, it also reduced the severity and duration of attacks, the need for open-label C1-INH rescue medicine, and the number of days with HAE swelling (7). Similar findings were observed in a few other uncontrolled clinical studies (36–38).

Dosage

In USA, C1-INH (Cinryze®) is FDA-approved for LTP in adolescents and adults at a dose of 1000 units every 3 or 4 days. Other C1-INH products (Berinert® and Cetor®) with different dosing and administration strategies have been used outside USA (39). No controlled clinical trials to support efficacy for the use of Cetor® or Berinert® in LTP have been performed.

Adverse effects

The side-effects reported in published controlled trials are minimal. However, this may be limited by relatively short observation time. In Waytes' study, the total time period of prophylactic treatment for all patients was $6 \times 17 = 102$ days ($< 1/3$ treatment year). There were no side-effects mentioned (17). In the most recent study of Cinryze®, the total period of prophylactic treatment for all patients was $22 \times 12 = 264$ weeks (= 5.1 treatment-years) (7). Three adverse events (pruritus and rash, light-headedness, and fever) were classified as possibly related to the study drug. Two of the 22 patients had an increase in attacks, and one had no response during the period of treatment with C1-INH concentrate. In an observational study, C1-INH concentrate was prescribed for 14 patients as LTP (37). A total of 137 treatment-years were analyzed. Ten of the 14 patients experienced an increase in attack frequency, or more C1-INH concentrate was required to control the disease. Furthermore, rapidly developing attacks and multilocation skin swellings have been observed. There are also concerns about infection at injection site and intrinsic infectivity risk of human blood products; however, as for any chronic user of blood products, hepatitis B vaccination is advisable. Lastly, thrombosis associated with indwelling catheters used for the administration of LTP C1-INH has been reported. Long-term efficacy, tolerability, and safety of this treatment still require additional studies.

Only Cinryze® is approved for LTP in Europe and USA.

Acute treatment (AT) for attacks

Introduction

Acute treatment aims to resolve angioedema symptoms as quickly as possible. Evidence suggests that C1-INH concentrates, plasma-derived (Berinert®, Cinryze®, Cetor® and a third preparation no longer on the market) and recombinant (Rhu-cin®/Ruconest®), kallikrein inhibitor ecallantide (Kalbitor®), and bradykinin B2 receptor antagonist icatibant (Firazyr®)

are suitable for AT of HAE (7–12, 17, 40). There are no comparative (head-to-head) studies.

Clinical trials were necessarily designed to investigate efficacy in a relatively limited situation, namely timely treatment for established attacks, and with relatively limited outcomes. Therefore, they may not directly reflect 'real life' where symptoms are treated early or at prodromes and final outcomes are measured by quality of life, economic well-being, and cost-effectiveness. Information lacking can in part be obtained from observational studies, but with intrinsic limitations. Recommendations from these studies can be extrapolated when aligned with the evidence derived from controlled studies.

The design and results of the phase III trials are summarized in Tables 1 and 2.

Plasma-derived C1 inhibitors

Berinert® (CSL Behring), Cetor® (Sanquin), and Cinryze® (ViroPharma) are plasma-derived C1-INHs on the market at present. All three are prepared from fractionated plasma obtained from selected donors and are pasteurized: Cinryze® undergoes an additional nanofiltration safety step. pdC1-INHs are administered intravenously.

Recent double-blind, randomized placebo-controlled trials demonstrated superiority of Berinert® and Cinryze® over placebo. Cetor®, registered in 1997 in a few European countries, was never tested in clinical trials. Limited dose finding in the Berinert® trials suggests that higher doses (20 U/kg) may be superior to those traditionally used (500–1000 U; 7–10 U/kg), at least for established attacks. Median time to onset of relief was significantly shorter with C1-INH at a dose of 20 U/kg than that with placebo (0.5 vs 1.5 h), whereas with 10 U/kg, the time to onset of relief was only slightly shorter than that with placebo (1.2 vs 1.5 h). The secondary outcomes consistently supported the efficacy of the 20-U/kg dose (12). These positive findings were confirmed on larger number of treatments performed in the extension phase of the study (41). Data from the Cinryze® trial are consistent with this. The median time to the onset of unequivocal relief from an attack was 2 h in the subjects treated with C1-INH and 4 h in those given placebo: 21 of 35 (66%) subjects randomized to the drug, in addition to the initial 1000 U, received a second 1000-U dose of C1-INH after 1 h, supporting the need for a higher dose than 1000 units for the majority of subjects (7). Further support for the use of higher doses comes from a trial performed with a preparation of pdC1-INH no longer available on the market (17, 40). In this trial, 25 U/kg was statistically superior to placebo in resolving attacks in 11 patients who underwent 55 C1-INH and 49 placebo infusions.

Observational studies have confirmed the efficacy of C1-INH and suggest that given very early during attacks, including at prodromes, doses as low as 500 U can be efficacious (39, 42). In addition, these studies provided other important information that cannot be obtained from controlled trials (12, 38, 43–48). Efficacy is consistent at all sites, including laryngeal swellings. Training of patients to self-administer

Table 1 Phase 3 trials for acute treatment of hereditary angioedema: trial design

Trial	Drug	Dose	Age (years)	Number of participants (active arm vs comparator; M/F)	Number of attacks	Time (h)	Site of swelling
Waytes/Kunschak et al. (17, 40)	pdC1-INH	23–30 U/kg vs placebo i.v.	15–60 vs 7–70	18 (10/8) vs 18 (9/9)	70	5*	All†
Craig et al. (12)	pdC1-INH	20 vs 10 U/kg vs placebo i.v.	6–62 vs 13–72 vs 10–71	42 (28/14) vs 39 (26/13) vs 43 (30/13)	125	5‡	Abdominal or facial
Zuraw et al. (7)	pdC1-INH	1000 U + 1000 U after 1 h if required vs placebo i.v.	36.7 ± 17.9 vs 36.2 ± 13.8	35 (26/9) vs 33 (27/6) 23 of 25 participants in the active arm received 2000 units	68	4*	Abdominal or facial
Zuraw et al. (8)	rC1-INH	100 U/kg; 50 U/kg vs placebo i.v.	17–67 vs 20–59 vs 17–71	29 (13/16) vs 12 (4/8) vs 29 (8/21)	70	5*	All
Cicardi et al. (9)	Ecaltantide	30 mg s.c.	18–77 vs 11–57	36 (12/24) vs 36 (13/23)	72	8‡	All§
Levy et al. (11)	Ecaltantide	30 mg s.c.	15.98–72.77 vs 13.64–72.37	48 (11/37) vs 48 (20/28)	96	8‡	All§
Cicardi et al. (10)	Icatibant	30 mg s.c.	34.8 ± 9.8 vs 34.9 ± 11.4	27 (11/16) vs 29 (8/21)	56	6‡	All†
	Icatibant	30 mg s.c.	40.4 ± 13.6 vs 41.9 ± 12.4	36 (12/24) vs 38 (15/23)	74	6‡	All†

*From onset.

†Open-label active treatment for potentially life-threatening laryngeal attacks.

‡From moderate/severe intensity.

§Open-label active treatment for severe upper airway compromise.

C1-INH is safe and improves symptom control. Reports on the use of pdC1-INH in pregnancy, lactation, very young children, and babies provide unique evidence for the safety and efficacy of this treatment in these critical subgroups of HAE patients (6, 47–50).

Safety

Available data from both controlled and noncontrolled studies do not suggest any safety issue (51, 52). General concern over transmission of blood-borne infections, inevitable when using human plasma-derived products, needs to be taken into account but has not been confirmed by experience (53). HCV transmission had been reported with a preparation no longer on the market, before the introduction of virucidal procedures and virus-screening methods (54).

Allergic/pseudo-allergic systemic reactions have been reported in a few patients. (55) When documented, they represent the only absolute contraindication to C1-INH. Immunogenicity to pdC1-INHs has not been reported (56).

Beriner[®] is approved in Europe for self-administration to treat all acute attacks and in USA to treat facial and abdominal attacks. Cinryze[®] is approved in Europe to treat all acute attacks.

Recombinant human C1 inhibitor

The rhC1-INH (Ruconest[®] in Europe, Rhucin[®] in USA, Pharming Group NV) is expressed in the mammary gland of transgenic rabbits (57). The main difference between rhC1-INH and pdC1-INH is the degree of glycosylation, which is lower in the former, related to its production in a heterologous system. Accordingly, rhC1-INH is cleared from the circulation faster, resulting in a shorter mean half-life (3 vs > 24 h) (47, 58, 59). The two products are equipotent: one unit of rhC1-INH is equivalent to 1 unit of pdC1-INH.

In two placebo-controlled studies, rhC1-INH at 100 (29 patients) and 50 (12 patients) U/kg body weight resulted in a significant reduction in the beginning of symptom relief (66 and 122 min) compared with saline (29 patients, 495 min). Additionally, the time to minimal symptoms was significantly shorter in patients receiving rhC1-INH (266 with 100 units and 247 min with 50 units) compared with those receiving saline (1210 min). Therapeutic failure occurred in 59% (17/29) of the saline group compared with 0% (0/12) of the 50-U/kg and 10% (3/29) of the 100-U/kg groups (8). Results from the open-label extensions of these studies have not yet been published: presentations at meetings suggest that rhC1-INH remains equally effective upon repeated treatments (EA-ACI London, June 6, 2010).

Safety

One healthy volunteer with undisclosed rabbit allergy experienced anaphylaxis after administration of rhC1-INH, suggesting that this treatment is unsuitable for patients with proven rabbit allergy. Patients should be screened by skin prick testing or serum-specific IgE to rabbit epithelium prior to prescribing rhC1-INH (8). No evidence of IgG or IgE antibody formation to rabbit, milk, or C1-INH has been seen in repeat

Table 2 Phase 3 trials for acute treatment of hereditary angioedema: results.

Trial	Drug	Design	Outcome measures	Time to outcome (active vs placebo) mean (sd)	Significance
Waytes/Kunschak et al. (17, 40)	pdC1-INH (Immuno-Baxter)	Double-blind, randomized, placebo-controlled*	Time to relief (h)	7.62 (7.08) vs 15.35 (8.31)†	P = 0.007
Craig et al. (12)	pdC1-INH (Berinert®)	Parallel-group randomized, double-blind placebo-controlled‡	Time to resolution (h)	23.98 (14.81) vs 34.58 (13.6)†	P = 0.09
			Time to onset of reliefs (h)	0.5 (0.17–24) vs 1.17 (0.17–24)	P = 0.2731 (10 U vs placebo)
				vs 1.5 (0.2–24)¶	P = 0.0025 (20 U)
Zuraw et al. (7)	pdC1-INH (Cinryze®)	Double-blind, randomized, placebo-controlled*	Time to complete resolution (h)	4.92 (0.47–1486) vs 20 (0.47–1486)	P = not reported
				vs 7.79 (0.33–1486)¶	P = 0.237
			Time to onset of relief (h)	2 vs >4¶	P = 0.02
			Complete resolution (h)	12.3 vs 25¶	P = 0.004
Zuraw et al. (8)	rC1-INH (Rhucin®/Ruconest®)	Double-blind, randomized, placebo-controlled	Time to onset relief (h)	1.1 (1.0–2.03) vs 2.03 (1.2–2.25) vs 8.25 (4.08–7.66)**	P < 0.01 (100 U vs placebo)
					P = 0.013 (50 U)
					P ≤ 0.01 (100 U)
					P = 0.01 (50 U)
Cicardi et al. (9)	Kallikrein inhibitor (Ecallantide/Kalbitor®)	Double-blind, randomized, placebo-controlled*	Time to minimal symptoms (h)	4.43 (4.03–8.17) vs 4.12 (4.03–8.07) vs 20.2 (25.2–25)**	P = 0.004
			Treatment outcome score (TOS) at 4 h	50 (0–100) vs 0 (0–100)††	P = 0.01
			Mean symptom complex severity score (MSCS: change from 0 to 4 h)	–1.00 (–1.50 to 0.0) vs –0.50 (–1.0 to 0.00)††	P = 0.01
			Time to onset relief (h)	2.75 (1.38 to >4) vs >4 (2.25 to >4)††	P = 0.14
Levy et al. (11)	Kallikrein inhibitor (Ecallantide/Kalbitor®)	Double-blind, randomized, placebo-controlled*	(MSCS: change from 0 to 4 h)	–0.8 (0.6) vs –0.4 (0.8)	P = 0.01
			TOS	53.4 (49.7) vs 8.1 (63.2)	P = 0.03
Cicardi et al. (10)	Bradykinin B2 receptor blocker (Icatibant/Firazyr®)	Double-blind, randomized, placebo-controlled	Time to first symptom improvement (h)	0.8 (0.5–2) vs 16.9 (3.2–NA)	P < 0.001
			Time to clinically significant relief (30–50% improvement; h)	2.5 (1.1–6) vs 4.6 (1.8–10.2)	P = 0.14
			Time to almost complete relief (90% improvement; h)	8.5 (2.5–31.5) vs 19.4 (10.2–55.7)	P = 0.08
			Time to first symptom improvement (h)	0.8 (0.4–1.4) vs 7.9 (1.1–NA)	P < 0.001
			Time to clinically significant relief (h)	2 (1–3.5) vs 12 (3.5–12.4)	P < 0.001
			Time to almost complete relief (h)	10 vs 51	P < 0.001

*Active comparator rescue at 4 h.

†Mean (standard deviation).

‡Crossover at 4 h if required: placebo to 20, 10–10, 20 U/kg to placebo.

§Set to 24 h if rescue medication received.

¶Median (range)/rescue (Cinryze) or crossover (Berinert®) at 4 h.

**Median (95% confidence interval).

††Median (interquartile range).

dosing studies. However, long-term data on larger populations are required to confirm the safety of the product. There are no data in pregnancy or in breastfeeding.

Ruconest[®] is approved in Europe for treatment for all acute attacks.

Kallikrein inhibitor ecallantide

Ecallantide (Kalbitor[®]; Dyax USA), a recombinantly produced and engineered small protein based on the first Kunitz domain of human tissue factor pathway inhibitor, is a potent and selective inhibitor of plasma kallikrein, the enzyme that cleaves high-molecular-weight kininogen, to release the nonapeptide bradykinin (60). Ecallantide is given subcutaneously in three 1-ml doses (total 30 mg) (61).

Two recent double-blind, placebo-controlled studies assessed its efficacy and safety in acute attacks at any location in 160 HAE patients over 10 years of age. Differences between ecallantide and placebo were assessed at 4 h from treatment using two different measures of patients' reported outcomes. The results of the two studies demonstrated a significantly higher improvement in both scores in the ecallantide-treated group (9, 11). Integrated analysis of these studies demonstrated efficacy of ecallantide at all attack locations (62). The results of open-label extension phase of the studies have been published in part and suggest that the majority of patients benefit from a single dose of ecallantide, and in 29%, a second dose may be necessary, mostly within 6 h, owing to incomplete efficacy (11).

Safety

Hypersensitivity (including anaphylaxis) is a known risk of ecallantide treatment for acute HAE attacks. Among a total of 255 treated patients by either i.v. or s.c. route, 14 (5.5%) experienced hypersensitivity reactions, including possible anaphylaxis (2.7%). Of the 187 patients treated with subcutaneous ecallantide, three experienced hypersensitivity, including anaphylaxis (1.6%) (63).

Ecallantide (Kalbitor[®]) is approved in USA for treatment for acute attacks with a boxed warning in the labeling, stating that the drug should be administered only by a healthcare professional who has medical support to manage anaphylaxis and HAE (64).

Seroconversion with IgG production to either ecallantide, Pichiapastoris, or both has been reported with a frequency below 10% of treated patients. The clinical significance of these antibodies is still controversial, and postmarketing surveillance will be necessary to gain further insights.

Bradykinin B2 receptor antagonist icatibant

Icatibant (Firazyr[®]; Shire), a synthetic decapeptide containing five nonproteinogenic amino acids, is a stable, selective bradykinin B2 receptor antagonist (65). It is given subcutaneously with a single injection of 30 mg (66). In two recently published multicenter clinical trials, FAST 1 and 2, patients with cutaneous and abdominal attacks were randomized to icatibant 30 mg or comparator. In FAST 1,

the comparator was placebo, and in FAST 2, the comparator was oral tranexamic acid. Laryngeal attacks were treated open label with icatibant. Time to significant symptom relief (reduction in symptom severity measured by visual analogue scale (VAS) $\geq 30\%$ of pretreatment value) was 2.5 h with icatibant vs 4.6 h with placebo in FAST 1 and 2.0 h with icatibant vs 12.0 h with tranexamic acid in FAST 2. The difference measured in the FAST 2 was statistically significant, while in FAST 1, it was not. Similarly, the time to almost complete (VAS change $\geq 90\%$) resolution was shorter with icatibant than with the comparator in both studies, 8.5 vs 19.4 h in FAST 1 and 10.0 vs 51.0 in FAST 2, but statistically significant only in the latter (10). An additional double-blind study (FAST 3) has been completed. This trial has been reported to show statistically significant superiority of icatibant over placebo (67). Open-label studies have shown benefit in multiple treatments for attacks at all sites. Approximately 10% of patients require a second dose for re-emergent symptoms, usually 10–27 h after the initial treatment (68).

As for other new drugs mentioned here, there are little published data on the open-label phase of the studies, particularly on outcome of laryngeal attacks. Based on available reports at meetings, icatibant shortens time to resolution for laryngeal attacks. Recurrence of symptoms, not necessarily at the same site, requiring a second injection of icatibant occurred around 10% and a third injection in 1% (69).

No immunogenicity or loss of efficacy was observed after up to 110 treatments in 118 patients (68).

Safety

No relevant safety concerns have arisen with the use of icatibant. The only side-effect consistently registered by 90% of treated patients is transient local pain, swelling, and erythema at the injection site. IgG and IgE production against icatibant has not been reported.

Icatibant (Firazyr[®]) is approved in Europe and USA for self-administration to treat all acute attacks.

Consensus and recommendations

While a number of previous consensus statements have been published (5, 6, 69), this conference attempted to readdress the issues by using an evidence-based approach (70, 71). Consensus reported here indicates that the majority of the conferees believed that the evidence supported the recommendation. Voting was restricted to those conferees who were not employed by industry, and, as physicians, had the responsibility for treatment prescription. The levels of evidence for recommendations are given according to the definitions suggested by the GRADE working group (72).

Goals of HAE treatment

HAE is a rare disease associated with significant morbidity and mortality (73). The following consensus statements were unanimously agreed upon:

1. Reducing morbidity and mortality in HAE must begin with early and accurate diagnosis.
2. HAE patients should have a specialist familiar with the disease involved in their care.
3. Treatment for HAE must be individualized to patient's needs and request to provide optimal care and restore a normal quality of life to the patient.

HAE disease scoring

To foster better recognition of attack events and promote the ability to compare data across different studies, a simplified disease-scoring instrument was discussed. The intent of this instrument was to define a minimal set of objective parameters, adapted to a variety of formats (electronic or manual patient self-reporting instruments) to be collected about angioedema attacks.

There was unanimous consensus regarding the following:

4. An effort must be made to ensure at least a minimal level of data consistency between different data collection instruments so that results can be compared across multiple systems.
5. The following minimal data set should be obtained for all acute attacks of angioedema:
 - 5a. Day and time of symptoms onset
 - 5b. Location of swelling
 - 5c. Severity score based on impact of swelling on patient performance
 - 5c.1. no limitations (mild)
 - 5c.2. able to perform activities, but with limitations (moderate)
 - 5c.3. unable to perform activities (severe)
 - 5d. Medical outcomes
 - 5d.1. called or was seen by a physician
 - 5d.2. went to an emergency department (if so, length of visit)
 - 5d.3. was admitted to the hospital (if so, length of stay)
 - 5e. Treatment given
 - 5e.1. type (name and dose)
 - 5e.2. time treatment started
 - 5f. Resolution of symptoms
 - 5f.1. time when symptoms began to improve
 - 5f.2. time when symptoms were totally resolved
6. This set of parameters should be collected for all angioedema attacks.
7. HAE patients should see their specialist physician on a regular basis and no less than once a year.
8. Annual health-related quality of life questionnaire is recommended.
9. Any angioedema attack in HAE patients can become disabling and/or life-threatening: therefore, all patients with HAE owing to C1-INH deficiency, even if still asymptomatic, should have access to at least one of the specific medicines, plasma-derived and recombinant C1-INHs, icatibant, and ecallantide, which obtained high grade of evidence from the above-mentioned trial for their efficacy in treating acute attacks 'on demand'.
10. Whenever possible and allowed by drug-specific summary product characteristics, patients should have the on-demand medicine to treat acute attacks at home and should be trained to self-administer these medicines. This recommendation has a low level of evidence because it is based on observational studies showing higher efficacy of early on-demand home treatment *vs* hospital treatment for angioedema attacks (38, 39). Nevertheless, it is very unlikely that controlled studies will be organized to test the appropriateness of this recommendation whose level of evidence will be reinforced by large, prospective observational data.
11. All attacks, irrespective of location, are eligible for treatment as soon as they are clearly recognized by the patient, ideally before visible or disabling symptoms develop. This recommendation has high level of evidence provided by controlled studies (9–12), showing that all the medications tested in these studies for angioedema attacks shorten their duration and therefore the attack-related inability.
12. Patients should immediately report to the hospital if laryngeal symptoms persist following an initial treatment. This recommendation is based on clinical experience showing the unpredictability of the evolution of laryngeal edema. Testing this recommendation in controlled or observational studies seems clearly unethical.

Using the definitions suggested by the GRADE working group (72) to evaluate the overall quality of evidence, recommendations 9–12 can be categorized as 'net benefit' with intervention clearly doing more good than harm.

Prophylactic treatment for HAE owing to C1-INH deficiency

In addition to treating acute attacks of angioedema, patients with HAE owing to C1-INH deficiency may require prophylactic treatment. The goal of prophylactic treatment is either to reduce the likelihood of swelling in a patient undergoing a stressor or procedure likely to precipitate an attack (short-term prophylaxis) or to decrease the number and severity of angioedema attacks (LTP). The approach to short-term prophylaxis has been recently addressed in a consensus document (69) and was not further addressed at this meeting because no further studies have been subsequently published. The issue of LTP was discussed, and areas of consensus are enumerated.

The first area of LTP consensus concerned which patients are candidates for LTP.

13. There was unanimous consensus that on-demand treatment for acute attacks should be the initial goal for all

Treatment of acute attacks of angioedema in patients with HAE owing to C1-INH deficiency

Based on evidence provided by seven high-quality controlled studies (7–12, 17), clear and unanimous consensus was reached regarding recommendations for the treatment for acute attacks of angioedema:

patients because it may reach the goals of HAE treatment by avoiding mortality and reducing morbidity.

14. Unanimous consensus was also reached on the concept that long-term prophylactic treatment was appropriate for patients in whom on-demand AT was inadequate to minimize the suffering related to the disease.
15. The circumstances under which on-demand treatment of attacks should be considered inadequate and the patient switched to LTP engendered considerable debate, and no unanimous consensus could be achieved. There are in fact no studies specifically designed to assess the net value of risk–benefit balance of LTP vs on-demand treatment. Therefore, with such a low level of evidence showing when LTP should be preferred to on-demand treatment of attacks, a slim majority of the conferees agreed that long-term prophylactic treatment was warranted if, in the opinion of the expert physician, the patient could not achieve adequate benefit from on-demand therapy of attacks. A substantial minority held the opinion that the definition of insufficient benefit from on-demand therapy of attacks must be based on objective evidence and suggested that this will be defined as more than 24 days per year with angioedema symptoms even if mild or more than 12 severe attacks per year.

The second area of consensus concerned the modalities of LTP. Existing trials and experience provide high levels of evidence for the efficacy of both attenuated androgens and plasma-derived C1 inhibitor, which is further supported by observational studies (7, 14, 16, 17, 22, 35, 38, 74, 75). Differently, trials showing the efficacy of antifibrinolytics were not confirmed in the general practice where the efficacy of these drugs appeared to be limited to a restricted number of patients as shown by observational studies (74, 75). For this reason, antifibrinolytics were not discussed in the consensus.

16. There was consensus that 17-alpha-alkylated androgens can be considered for LTP for patients who are above 16 years of age and nonpregnant or lactating women.
17. Consensus was reached that 17-alpha-alkylated androgens are not recommended for LTP when the patient cannot tolerate them or if the effective dose exceeds the equivalent of 200 mg danazol/day.
18. Consensus was reached that pdC1-INH can be considered for LTP without exclusion for all groups of patients.
19. Evidence suggests that 1000 units twice a week reduces attack rates only by 50%; higher doses may be necessary in some for better control. Thus, it is recommended that regimens of prophylactic pdC1-INH should be individualized to optimize the clinical response.

Areas that require additional investigation

Several areas were mentioned that require further investigation before consensus can be attempted. These areas include the following:

- Can implementation of aggressive early home on-demand treatment [also known as individual replacement therapy (39)] reduce the need for prophylactic treatment in patients

who do not achieve sufficient benefit from standard on-demand treatment?

- Is it better to increase the dose of C1-INH or the frequency of administration in patients who are receiving long-term prophylactic C1-INH who continue to swell?
- Is it possible to identify biomarkers that will predict which drugs will work best for individual patients?
- What is the best instrument to use to monitor response of acute attacks to therapy?
- Will a specific quality-of-life survey for HAE add to how we monitor, treat, and care for HAE patients?
- What are the optimal strategies for treating children or pregnant women?
- How should patients with HAE and normal C1-INH be diagnosed and managed?
- How should patients with acquired C1-INH deficiency be managed?
- How should patients with other types of nonhistaminergic angioedema be managed?
- How should acute attacks of ACE-I-mediated angioedema be treated?

Conclusion

Enormous progress has been made in the understanding of the pathophysiology of C1-INH deficiency and in the treatment of HAE. It is clear that long-established treatment guidelines formulated prior to these advances need to be updated. Specifically, there was unanimous consensus that a more pro-active patient-centric approach to HAE treatment needs to be implemented. While recognizing that different areas of the world have unique patterns of care, based on different healthcare delivery systems, it is our hope that the consensus statements reviewed here will provide useful means to update the practice parameters of physicians caring for HAE patients everywhere. Finally, there was agreement that these consensus statements would need to be revisited as soon as additional scientific evidence becomes available.

Conflict of interest

MC: Dr. Cicardi has served as consultant for CSL Behring, Dyax, ViroPharma; Pharming, Jerini/Shire, BioCryst. Dr. Li has served as a speaker for Dyax, CSL Behring, Shire, and ViroPharma; and as a consultant for CSL Behring, Dyax, Jerini/Shire, ViroPharma; and as an investigator for clinical trials sponsored by CSL Behring, Dyax, Jerini/Shire, Pharming, and ViroPharma. Dr. Craig is a speaker for CSL Behring, Dyax, Shire and Viropharma. He is a consultant for CSL Behring and Dyax. He has done research for CSL Behring, Dyax, Pharming, Shire and Viropharma. Dr. Caballero has received a speaker and consultancy fee from Shire and Viropharma Pharmaceuticals, funding for travel and meeting from CSL-Behring and Shire and has participated in clinical trials for Dyax, Pharming, CSL-Behring, Jerini AG and Shire. Dr. Bork is a consultant for CSL Behring, Shire and Viropharma. Dr. Longhurst has received funding for research and staff support from CSL Behring, Shire and

Pharming. She is a consultant for CSL Behring, Shire and Swedish Orphan. She is a speaker for CSL Behring, Shire, Swedish Orphan and Viropharma. Dr. Zuraw: Consultant to ViroPharma, Dyax, Shire, Santarus, CSL Behring, BioCryst Research grants from Shire and Pharming.

Supporting Information

Additional Supporting Information may be found in the online version of this article found at: <http://www.wileyonlinelibrary.com>

Data S1. Validated instruments for assessing severity of acute HAE attacks.

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Appendix

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Validated instruments for assessing severity of acute HAE attacks

Multiple questionnaires have been used to assess the impact of HAE, by measuring attack severity, quality of life and social economic impact of HAE. Many of these questionnaires are not validated and therefore we will mainly focus on those that received validation. One of the most commonly used instruments uses the visual analogue scales (VAS).(1)

HAE-specific VAS were developed to assess symptoms of an acute angioedema attack in clinical studies with recombinant human C1-INH (rhC1-INH), bradykinin B₂ receptor antagonist (icatibant), and pdC1-INH (Cinryze®).(2-5) With rhC1-INH patient-completed scales were used to assess the intensity of symptoms at abdominal, oro-facial-pharyngeal-laryngeal, peripheral, and urogenital attack locations. For each of these anatomical locations a series of symptom-related questions were asked, and patients responded by marking a line on a 100 mm scale with descriptive anchors at each end. To allow comparisons between anatomical locations, the last question for each location was an overall severity VAS item of “How severe are the angioedema symptoms now for this location” (identical wording for all four location VAS instruments) with response anchors of ‘no symptoms at all’ and ‘extremely disabling’. To assess the course of attack symptoms, patients completed the VAS scores prior to treatment and at regular intervals thereafter.

A similar instrument was used in the Cinryze® clinical trials (CHANGE-2). The instrument included 5 VAS to assess gastrointestinal, genitourinary, facial, respiratory and extremity swelling.(3) VAS was also used as a primary endpoint in the icatibant trials.(2, 5)

HAE-specific VAS validation demonstrated comprehensibility, relevance and suitability for use in clinical trials of acute HAE of the VAS. A psychometric evaluation, which is still unpublished, confirmed that a 20mm change in the overall severity VAS item indicated a minimal clinically important difference which could be used to define onset of relief.

In some other clinical trials, an alternate validated questionnaire instead of VAS was used to assess the onset of relief. In pdC1-INH Berinert study IMPACT-1, and in a study done in the mid 1990s by Waytes et al the time to onset of relief was determined by a series of questions in which a reduction in severity was defined as the time to first symptom improvement. This endpoint has been used successfully in multiple clinical trials and has been well validated.(6-8)

In the kallikrein antagonist (ecallantide) phase III trials, 2 different disease-specific, patient-reported validated instruments were used. One was the response to therapy (Treatment Outcome Score-TOS) and the other a severity of symptoms score (Mean Symptom Complex Severity Score-MSCS). The TOS was a composite treatment outcome score that ranged from +100 (significant improvement of symptoms) to -100 (significant worsening of symptoms). The MSCS measures the symptom sites and severity before and after therapy. The values range from 0 to 3 with 0= no symptoms and 3= severe symptoms. Both the TOS and the MSCS are specifically designed to assess severity of symptoms of HAE and response to an intervention.(9-10)

Unfortunately, instruments to follow the severity of HAE over time and the impact or burden of disease on the patient have been limited by the variable expression of disease manifestation and the lack of baseline symptom follow up in between acute attacks. Most study instruments have been adapted from validated questionnaires used in other chronic illnesses and are not specific for HAE. Validated instruments used in recent longitudinal studies include SF- 36, Dermatology Life Quality Index (DLQI) and the Work Productivity and Activity Impairment-General Health Questionnaire (WPAI-GH). WPAI-GH is a commonly used survey to determine the impact of a chronic illness on patients' productivity. It is composed of 6 questions that reflect back on the past week. Use for a longer retrospective time would invalidate the survey mainly because of reduced recall. This 7 days duration limits the utilization in HAE due to the episodic nature of the disease; however, it was recently used in a study on the economic burden of HAE to assess productivity limitations in a cohort of patients.(11)

SF-36 and its modifications SF-15 and SF-12 are widely used and validated instruments, not specific for HAE, to assess quality of life in a chronic disease. Recent studies using SF-36 demonstrated that patients on androgens analyzed retrospectively and having adverse events or poor response to them had an improvement of their SF-36 when converted over to C1-INH.(3, 12)

Dermatology Life Quality Index (DLQI) (13-15) is another QOL instrument, but validated for skin disorders.(13) The instrument is not specific for HAE, nor is it designed for assessing abdominal pain, but has been utilized for HAE successfully by Bygum et al. They assessed home therapy with C1-INH by both SF-36 and the DLQI and both instruments demonstrated that home therapy improved QOL significantly.(14) A modified version (CDLQI) for children exists, but it has not been utilized in HAE.(15)

Unmet needs

When assessing a HAE patient, it is important to know if the disease has been well controlled in the last week to months. The instrument should be easy to read, with only a handful of questions, with limited replies. In addition, the end result should be a composite score that can be compared on serial visits to determine if treatment needs to be modified. The instrument should be similar to the Asthma Control Test that was developed and validated for the management of asthma (16). We call on the HAE experts to develop a similar score for HAE disease.

Although, as noted above, validated HAE attack severity score systems have been developed, no study has ever compared these instruments and no consensus exists on which of them provides the best data. There is also a great need for a validated HAE-specific QOL instruments, two such instruments are under development and they are expected to be soon available (von Mackensen et al.: Health-related quality of life (HRQoL) in patients with hereditary angioedema - Development of a disease-specific questionnaire (HAE-QoL). 7th C1-INH Deficiency Workshop. 2011. Budapest, Hungary. 20-5-2011; Prior N, Remor E, Gomez Traseira C, Pedrosa M, Lopez Serrano C, Caballero T. Development of a specific questionnaire for the assessment of health-related

quality of life in adult patients with hereditary Angioedema due to C1 inhibitor deficiency (HAE) and cross-cultural validation proposal. *J Allergy Clin Immunol* 2008;121:S106 (Abstr.); Prior N, Caballero T, Gómez-Traseira C, Gayá F, Caminoa M, Remor E, and the DV-IHAE QoL group. Pilot Study for the Development of an International Specific Questionnaire for the Assessment of Health-Related Quality of Life in Adult Patients with Hereditary Angioedema due to C1 inhibitor Deficiency (IHAE-QoL): preliminary results. *J Angioedema* 2011; 33 . 7th C1-inhibitor Deficiency Workshop, Budapest, Hungary 2011 (Abstr.)). A study comparing different treatment outcome instruments in HAE should be carried out in order to be able to choose the most appropriate tool to assess drug efficacy and acute attack severity. As health care providers caring for HAE patients we should encourage the use of uniform instruments in all future studies so that the efficacy of one agent can be compared to another in a logical and evidence-based fashion.

Antifibrinolytics

Two antifibrinolytic agents, epsilon amino-caproic acid and tranexamic acid, have been shown to be effective in LTP of HAE. In 1972 a double-blind placebo-controlled cross-over study with 16 g epsilon amino-caproic acid per day versus placebo was performed in 5 patients.(17) Four of the 5 patients benefited significantly from the therapy with epsilon amino-caproic acid. Another double-blind placebo-controlled cross-over trial was performed in 18 patients with 3g tranexamic acid daily versus placebo for a 3-months period each.(18) Seven of the 18 patients had a complete or almost complete cessation of attacks during the drug-trial period whereas the attack frequency did not change during the placebo trial. Four more patients had some attenuation in the frequency and a reduced severity of the attacks. In one patient tranexamic acid was ineffective. Observational studies in adults indicate that the efficacy of tranexamic acid as LTP for HAE is much lower than that of attenuated androgens, and very few patients successfully remain on this treatment.(19-20) For this reason prescription of these drugs is now limited to those patients in whom other prophylactic treatments cannot be used.

Contraindications

Antifibrinolytic agents are contraindicated in presence of active thromboembolic disease; history of thrombosis or thromboembolism; intrinsic risk of thrombosis or thromboembolism. Doses should be adjusted in patients with renal impairment. Adverse events were not observed in animal reproduction studies, but there are no adequate and well-controlled studies in pregnant women.

Adverse effects

Nausea, vomiting, diarrhea, myalgia, and muscle weakness (including muscle enzyme elevation and rarely rhabdomyolysis) have been reported as well as fatigue and orthostatic regulation disturbances.

Monitoring

Regular follow-up visits every six months are recommended. Screening should consider assessment of renal function, retinal changes and glaucoma. Serum creatine phosphokinase and aldolase; liver and renal function, as well as urinalysis should be checked regularly.

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