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Administration of conestat alfa, human C1 esterase inhibitor and icatibant in the treatment of acute angioedema attacks in adults with hereditary angioedema due to C1 esterase inhibitor deficiency. Treatment comparison based on systematic review results

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Abstract

Introduction: Hereditary angioedema (HAE) is a genetic disease caused by C1-esterase inhibitor deficiency, characterized by recurrent attacks of intense, massive, localized subcutaneous oedema that can involve all parts of the body. The aim of this study is a comparison of the clinical effectiveness of conestat alfa, human C1 esterase inhibitor (C1INH) and icatibant in the treatment of acute angioedema attacks in adults with HAE.

Materials and methods: A systematic review of literature published up to May 2012 was performed to assess the efficacy and safety of conestat alfa, C1INH and icatibant in the treatment of acute angioedema attacks in adults with HAE. Databases were searched at MEDLINE (PubMed), EMBASE and Cochrane. The general search structure was designed as a combination of keywords or synonyms: (hereditary angioedema) AND (conestat alfa OR human C1 esterase inhibitor concentrate or synonyms OR icatibant). Only randomized clinical studies were selected.

Results: Systematic review yielded no clinical trials directly comparing the therapeutic options mentioned. Two randomized clinical trials were found which compared each of the following: conestat alfa, C1INH and icatibant with placebo. Based on the gathered evidence it was demonstrated that taking any of the medicinal substances mentioned in the treatment of acute angioedema attack results in a shorter time to the start of symptom relief and the time to reduce symptoms, the probability of treatment response after 4 hours is increased and the safety profile is comparable to placebo.

Conclusions: Due to the significant heterogeneity of the identified trials, the scientific evidence available was insufficient to identify the most effective therapeutic option in the treatment of acute oedemas in HAE.

Key words: conestat alfa, human C1 esterase inhibitor, icatibant, hereditary angioedema, C1 esterase inhibitor deficiency

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Introduction

Hereditary angioedema (HAE) is a genetically determined, autosomal dominant disease, caused by a deficiency in the complement component of protein - C1 inhibitor, resulting from mutation of the gene coding this protein [1–5]. Although angioedema is classified as a hereditary disease, 25% of new cases are caused by spontaneous mutations [5].

Improper function of C1 esterase inhibitor or its absence causes uncontrolled activation of the complement, kallikrein and fibrinolysis systems. Typical symptoms of HAE are intensive oedema of connective tissue, which may involve all parts of the body: the extremities, genitals, face, trunk, submucosal oedema of the upper airways or intestines, which may pose a real threat to life [1, 4, 6]. Unlike other types of oedema, hereditary angioedema does not manifest itself in pain, erythema or urticarial changes; and the appearance of symptoms of the disease is not connected with allergen. Furthermore, the symptoms of angioedema generally develop slowly (over 12–36 hours) [1].

According to statistics showing the prevalence of rare diseases in 2011, hereditary angioedema affects 1 case per 100,000 individuals [7]. As maintained by the clinical expert, the number of patients with HAE in 2011 in Poland was estimated at 236 people (children and adults) [8]. However, some sources (estimated values based on available sources for epidemiological data) have shown that there may be as many as 800–4000 people afflicted by this disease in Poland, but only 150 persons have been properly diagnosed with HAE. In the remaining patients, appropriate diagnosis has not been established, or they have not yet experienced an angioedema attack intense enough to be diagnosed as HAE [1, 9].

Treatment of acute angioedema attack depends on its localization and the intensification of its symptoms. According to some authors, acute attacks of angioedema localized peripherally (palms, feet, perineum) do not necessitate treatment, whereas attacks of severe angioedema that pose a threat to life (for instance, oedema of the face, airways or oedema localized in abdominal cavity) require initial administration of C1 esterase inhibitor (human or recombinant), bradykinin B2 receptor antagonists (icatibant) or kallikrein inhibitor (ecallantide). Additionally, old types of drugs are used: freshly-frozen plasma, anabolic drugs and antifibrinolytics [10, 11, 12, 14].

The main threat connected with hereditary angioedema are fatal oedema attacks of the larynx [2, 4, 15]. Mortality due to acute angioedema attacks of the larynx and related respiratory disorders are estimated at 15–33% [16, 17]. Hereditary angioedema also favours the occurrence of coexistent disorders such as depression and anxiety disorders. Moreover, frequent use of analgesic drugs during acute angioedema attacks may lead to drug dependence. The disease significantly restricts patients' life quality as attacks result in absence from work or school, they are painful and disfiguring, and they require treatment and seeing a doctor [17–19]; moreover, relatively frequent hospitalization involves additional financial outlay [17, 19]. Therefore, hereditary angioedema poses a serious health and social problem [20]. Consequently, there is a need to introduce new drugs that would allow patients to control effectively the symptoms of the disease, i.e. rapid reduction of the symptoms of angioedema attack before their intensification, with the slightest risk of the occurrence of undesirable effects.

Conestat alfa (recombinant C1 esterase inhibitor, rhC1INH) is produced by using recombinant DNA technology in the milk of transgenic rabbits that have received genes coding human C1INH. The amino acid sequence of a recombinant protein and its inhibitory properties are identical to a naturally occurring protein [20, 21].

The aim of this study is to compare the clinical effectiveness of conestat alfa with alternative means of therapeutic treatment used in Poland: human C1 esterase inhibitor and icatibant.

Material and methods

In order to assess the clinical effectiveness of rhC1INH compared to human C1INH and icatibant, a systematic review of medical literature published before 8 May 2012 concerning the use of the mentioned substances for the treatment of acute angioedema attacks, was undertaken. Databases were searched at MEDLINE (PubMed), EMBASE and Cochrane. Additionally, other databases were searched such as clinical trials registers, conference reports and websites of the European Medicines Agency, Food and Drug Administration and other agencies dealing with the evaluation of medical technologies. The undertaken review was in conformity with evidence-based medicine (EBM) [22] recommended by the Cochrane Collaboration [23] and the Agency for Health Technology Assessment in Poland [24]. Our search strategy included among others the following keywords connected with the use of the Boolean operators: ("Hereditary Angioedema" OR "angio-oedema" OR "angioneurotic syndrome" OR "Angioneurotic

Oedema" OR "Quincke oedema" OR "giant urtica") — in reference to population AND ("Ruconest" OR "Rhucin" OR "rhC1INH" OR "rHuC1INH" OR "conestat alfa" OR "recombinant human C1 inhibitor") in reference to conestat alfa or ("Berinert" OR "human C1 esterase inhibitor concentrate" OR "plasma derived C1 esterase inhibitor concentrate") for human C1INH or ("Firazyr" OR "icatibant") in reference to icatibant. The results were limited to human trials, and in order to identify randomized clinical trials, methodological filters were applied (Clinical Trials, Randomized Clinical Trials, Controlled Clinical Trials). Publications in English, Polish, French and German were searched. The review included all randomized clinical trials in which the effectiveness and safety of the use of the above substances in the treatment of angioedema were assessed. The process of trial selection consisted of two stages (exclusion on the basis of titles and abstracts and then on the basis of full texts based on earlier defined inclusion and exclusion criteria), and it was performed by two analysts working independently.

In order to compare the clinical effectiveness of conestat alfa to icatibant and a natural C1INH in the treatment of acute HAE attacks, the results for clinically significant endpoints that are important from the point of view of the patient and the doctor have been presented: time to onset of symptoms relief, time to appearance of "minimal symptoms" of the attack, and the proportion of patients who responded to treatment less than 4 hours after intervention (Table 4). The results for parameters such as "time to" in each case were given in the form of median defining time after which half of the patients had reached a given clinical state. For dichotomous parameters (the proportion of patients who responded to treatment less than 4 hours after intervention and undesirable effects) relative benefit (RB) or relative risk (RR) was calculated, which is the quotient of likelihood of occurrence of a given event in the two therapeutic groups.

To assess safety profiles, the risk of occurrence of any treatment-related acute and serious side effects was analysed. Furthermore, death risk in the study groups was assessed, and undesirable effects for which statistically significant differences between investigational branches were shown, were presented.

Results

As a result of a systematic review of databases, after exclusion of publications not corresponding in terms of subject or methodology, two randomized clinical trials concerning rhC1INH compared to placebo were found (the results of the individual trials were provided by the company Swedish Orphan Biovitrium Sp. z o. o.): C1 1205-01 [25] and C1 1304-01 [26]. Moreover, a study including the overall results of these clinical trials was found [21]. Additionally, the following studies were found: two studies concerning the comparison of icatibant to placebo: FAST-1 [27–29] and FAST-3 [30, 31]; and two studies into the comparison of natural C1 esterase inhibitor concentrate: I.M.P.A.C.T-1 [32–38] and the Waytes study 1996 [39, 40]. No clinical trials concerning direct comparisons of the analysed interventions were found. All of the studies that qualified for this review concerned the comparison of the above-mentioned substances to placebo. With reference to their methodology, the studies are double-blind, randomized, parallel-group clinical trials. The most important information concerning the individual studies is presented in Table 1. The included studies were assessed with respect to methodological correctness based on the five-point Jadad scale [41] (Table 2). Due to differences in the clinical characteristics of patients included in the individual studies, slight differences in the definitions of endpoints or differences in the evaluation period, the possibilities of conducting a direct quantitative comparison of the presented substances with the use of a common comparator have not been used (Table 1, 3) [42]. Only the results of the individual studies for very similar or identical endpoints have been compared. However, due to the above differences, the results of the comparison should be interpreted with great caution, and in each case attention should be paid to the definition of the endpoint used in any given study [22].

The results for all doses of the medicinal products analysed in the considered clinical trials have been presented (Table 4), but it should be mentioned that the recommended single doses of separate preparations administered in the symptomatic treatment of acute HAE attacks (in conformity with Summaries of Product Characteristics) are the following: 50 U/kg for conestat alfa [20], 30 mg for icatibant [43] and 20 U/kg for natural C1INH [44].

Time to onset of relief of symptoms

Time to onset of symptoms relief was approximately 2 times shorter, compared to placebo, in patients who were administered 50 U/kg of rhC1INH ($p < 0.001$) [25], and approximately 4–8 times shorter after administration of larger than recommended dose 100 U/kg of rhC1INH ($p < 0.003$)

Table 1. Characteristics of studies included in the systematic review

	C1 1205-01 [25]	C1 1304-01 [26]	FAST-1 [27–29]	FAST-3 [30, 31]	IMPACT 1 [32–38]	Waytes 1996 [39, 40]
Inclusion criteria	HAE; C1INH < 50% of predicted; age ≥ 12 years	HAE; C1INH < 50% of predicted; age ≥ 16 years	HAE; C1INH < 50% of predicted; age ≥ 18 years	HAE; C1INH < 50% of predicted; age ≥ 18 years	HAE; level C1INH - no data available; age ≥ 6 years	HAE; C1INH <30% of predicted; age ≥ 6 years
Location and severity of attack qualifying for inclusion	All locations; ≥ 50 mm measured in VAS	All locations; ≥ 50 mm measured in VAS	Excluded laryngeal oedema; ≥ 30 mm measured in VAS	Excluded severe laryngeal oedema; ≥ 30 mm measured in VAS	Abdominal cavity (excluded cutaneous oedema); face (excluded laryngeal oedema); size - no data available	All locations; size - no data available
Dosage; number of participants (n)	rhC1INH 50 U/kg, n = 12 rhC1INH 100 U/kg, n = 13 placebo, n = 13	rhC1INH 100 U/kg, n = 16 placebo, n = 16	Icatibant 30 mg, n = 27, placebo, n = 29	Icatibant 30 mg, n = 46, placebo, n = 47	C1INH: 10 U/kg, n = 40; C1INH: 20 U/kg, n = 43; placebo, n–42	C1INH: 25 U/kg, n = 18; placebo; n = 18
Moment of drug administration	< 5h	<5h	<6h	<6 h	Bd No data available	<5h
Evaluation period	First 4 h; measurements after 16h, 24h, 48h and at least once a day to minimal symptoms; 90 days for adverse events	First 4h; measurements after 16h, 24h, 48h and at least once a day to minimal symptoms; 90 days for adverse events	First 4 h every 30 minutes; mesurements after 5h, 6h, 8h, 10h, and between 12h and 15h, and then 3 times a day to relief of symptoms; visits after 2, 14 days and 5 and 24 weeks	First 4 h every 30 minutes, measurements after 5h, 6h, between 8h and 12h, and then 3 times a day to relief of symptoms, visits after 2, 14 days and 5 and 24 weeks	First 4 h after the intervention, 9 days for adverse events	24 h for adverse events

VAS — Visual Analogue Scale

Table 2. Jadad score for studies included

	C1 1205-01 [25]	C1 1304-01 [26]	FAST-1 [27–29]	FAST-3 [30, 31]	IMPACT 1 [32–38]
Was the study described as randomized?	+1	+1	+1	+1	+1
Was the study described as double blind?	+1	+1	+1	+1	+1
Was there a description of withdrawals and dropouts?	+1	+1	+1	+1	+1
The method of randomisation was described in the paper, and that method was appropriate (+1)/inappropriate(–1)?	–1	–1	–1	–1	+1
The method of blinding was described, and it was appropriate(+1)/inappropriate(–1)?	+1	+1	+1	0	0
Sum	3	3	3	2	4

Table 3. Definitions of endpoints in studies included in the systematic review

	C1 1205-01 [25]	C1 1304-01 [26]	FAST-1 [27–29]	FAST-3 [30, 31]	IMPACT 1 [32–38]	Waytes 1996 [39, 40]
Time to beginning of relief of symptoms	Reduction of oedema ≥ 20 mm in VAS compared to the initial state (for the first location where improvement was found)	Reduction of oedema ≥ 20 mm in VAS compared to the initial state (for the first location where improvement was found)	Reduction of oedema by 20––30 mm depending on the initial size; ≥ 30%	Reduction of oedema by 31 mm compared to the initial state 100 mm, by 21 mm for 30 mm, and by 68% for oedemas smaller than < 30 mm	First symptoms of improvement in the subjective assessment of the patient (no scale was used)	Onset of relief of symptoms during the first attack (no scale was used)
Time to minimal symptoms	All oedemas < 20 mm in VAS	All oedemas < 20 mm in VAS.	Oedema ≤ 10 mm in VAS	Oedema ≤ 10 mm in VAS	Complete improvement of all symptoms of oedema (including pain) in the subjective assessment of the patient	Complete relief of oedema during the first attack
Response to treatment	Proportion of patients, in whom oedema was reduced to ≤ 20 mm in VAS during 4h after the intervention	Proportion of patients, in whom oedema was reduced to ≤ 20 mm in VAS during 4h after the intervention	Proportion of patients, in whom oedema was reduced by 30% during 4h after the intervention	–	–	Proportion of attacks whose symptoms were reduced during 240 minutes after the intervention
Safety profile	Yes	Yes	Yes	Yes	Yes	No (only general mentioning of the most frequent actions)

VAS — *visual analogue scale*

[25, 26]. The use of icatibant at a dose of 30 mg made the above time twice ($p = 0.142$) [27–29] or approximately ten times ($p < 0.001$) [30-31] shorter compared to the time when given placebo. The observed differences between the studies were presumably the result of slight divergences between the definitions of endpoints and the characteristics of the included patients. Administration of natural C1INH concentrate at a dose of 20 U/kg made the time to onset of symptoms relief three times shorter compared to that seen with administration of placebo ($p = 0.003$) [32–38]. This observation was similar to the study results [39, 40] in which patients were given 25 U/kg of C1INH. However, when the patient took 10 U/kg of C1INH, the time to onset of symptoms relief was only slightly shorter

compared to that with placebo, and this difference was statistically insignificant [32–38].

Time to minimal symptoms

The results concerning time to minimal symptoms for individual substances were similar to those in the case of onset of symptoms relief (Table 4). Administration of 50 U/kg of conestat alfa instead of placebo made time to reduction of oedema to a size smaller than 20 mm 4.5 times shorter ($p < 0.001$) [25], and conestat alfa at a dose of 100 U/kg made this time approximately 3–4.5 times shorter ($p < 0.05$) [25, 26]. Icatibant at a dose of 30 mg made this time more than two times shorter ($p = 0.08$) [27–29] or approximately 4.6 times shorter ($p = 0.016$) [30, 31] compared to placebo. In patients who were administered C1INH concentrate at a dose of 20 U/kg, time to complete resolution of symptoms was nearly two times shorter than after administration of placebo ($p = 0.0237$) [32–38]. This observation was similar to the results of a study [39, 40] in which patients were administered 25 U/kg of C1INH. When the patient was administered 10 U/kg of C1INH, this time was made longer compared to placebo, but the difference between the groups was statistically insignificant [32–38].

Response to treatment after 4 hours

The probability of response to treatment in the group taking conestat alfa at a dose of 50 U/kg was 1.63 times higher than that seen in the placebo group ($p = 0.039$) [25], 1.59 ($p = 0.039$) [25] or 3 times higher ($p < 0.001$) [26] after administration of 100 U/kg of conestat alfa. Icatibant at a dose of 30 mg did not significantly increase the probability of obtaining response to treatment less than 4 hours after the intervention [27–29], whereas administration of 25 U/kg of C1INH concentrate in the study [39, 40] increased it by 7.72 times ($p < 0.05$) (Table 4).

Safety profile

Administration of conestat alfa at doses of 50 U/kg and 100 U/kg in the treatment of acute angioedema attack did not increase the risk of occurrence of any treatment-related acute or serious undesirable effects [25, 26]. In the research C1-1304-01 the relative risk (RR) of occurrence of any undesirable effect was four times smaller in the group taking 100 U/kg of rhC1INH than in the placebo group, RR = 0.25 (95% CI: 0.07; 0.84; $p = 0.02$) [26]. No death resulting from treatment-related undesirable effects was noted in any of the study groups [25, 26]. Administration of 30 mg of icatibant in the treatment of HAE attacks did not increase the risk of occurrence of any treatment-related acute or serious undesirable effects. The use of icatibant increased the risk of occurrence of undesirable effects in the place of its administration, RR = 3.49 (95% CI: 2.09; 6.57; $p < 0.0001$) [27–29] and gastrointestinal troubles, RR = 5.00 (95% CI: 1.33; 19.67; $p < 0.05$) [30, 31], but it decreased the risk of occurrence of acute undesirable effects, RR = 0.20 (95% CI: 0.05; 0.75; $p = 0.027$) [30, 31]. During the FAST-3 trial in the placebo group one case of death, which was the consequence of undesirable effects, was noted; however, it was discovered that these effects were not treatment-related. Administration of natural C1INH concentrate at a dose of 10 U/kg or 20 U/kg was not connected with a higher risk of occurrence of undesirable effects overall, neither serious nor treatment-related. C1INH concentrate at a dose of 20 U/kg decreased the risk of occurrence of any undesirable effects by more than two times, RR = 0.45 (95% CI: 0.22; 0.86; $p = 0.02$) and gastrointestinal troubles, RR = 0.34 (95% CI: 0.14; 0.84; $p < 0.05$) [32–38].

The use of all analysed therapeutic options in the treatment of acute angioedema attack was as safe as placebo (in reference to undesirable effects).

Discussion

It was shown on the basis of clinical trials that conestat alfa and its comparators, C1INH and icatibant, are clinically more effective than placebo in the treatment of acute attacks of hereditary angioedema, regardless of localization of oedema and prevalence thereof. The differences are statistically significant. The safety profile, based on the results of clinical trials, showed good tolerance by patients to the analysed substances. The lack of clinical trials to compare directly rhC1INH to the chosen comparators, and the lack of homogeneity between the gathered clinical trials and a common comparator — placebo, hinder the drawing of any conclusions concerning differences in the clinical effectiveness between the used therapies.

Therefore, the scientific evidence presented by the authors of this paper based on the analysed studies does not allow explicit indication of the best therapeutic option in the treatment of acute angioedema attacks.

It should be emphasized that the results for time to onset of symptoms relief, time to minimal symptoms, and response to treatment for natural C1INH [32–40] may be determined as the least reliable as they were based only on subjective

Table 4. Studies' results for time to beginning of relief of symptoms, time to minimal symptoms, response to treatment after 4 h

	Time to beginning of relief of symptoms			Time to minimal symptoms			Response to treatment after 4h
	Treatment group	Placebo	p	Treatment group	Placebo	p	Relative benefit
rhC1INH 50 j./kg [26]; min [95% CI]	122.0 [72.0; 136.0]	258.0 [240.0; 495.0]	<0.001	246.5 [243.0; 484.0]	1,101.0 [970.0; 1,494.0]	< 0.001	1,63 [1,04; 2,72]; p = 0,039
rhC1INH 100 j./kg [26]; min [95% CI]	68.0 [62.0; 132.0]	258.0 [240.0; 495.0]	0.001	245.0 [125.0; 270.0]	1,101.0 [970.0; 1,494.0]	0.04	1,59 [1,06; 2,73];p = 0,039
rhC1INH 100 j./kg [27]; min [95% CI]	61.5 [40.0; 75.0]	508.0 [70.0; 720.0]	0.003	480.0 [243.0; 723.0]	1,440.0 [720.0; 2,885.0]	0.005	3,00 [1,63; 6,67]; p < 0,001
Ikatybant 30 mg [28-30]; h [IQR]	2.5 [1.1; 6.0]	4.6 [1.8; 10.2]	0.142	8.5 [2.5; 31.5]	19.4 [10.2; 55.7]	0.08	1,44 [0,90; 2,38]; p > 0,05
Ikatybant 30 mg [31-32]; h [IQR]	1.6 [1.3; 2.5]	16.5 [3.6; 23.8]	<0.001	7.0 [5.0; 42.5]	33.9 [26.7; 50.5]	0.016	-
C1INH: 10 j./kg [33-39]; h [95%CI]	1.17 [0.17; 24.00]	1.50 [0.20; 24.00]	0.273	20.00 [0.47; 1,486.17]	7.79 [0.33; 1,486.17]	0.36	-
C1INH: 20 j./kg [33-39]; h [95%CI]	0.50 [0.17; 24.00]	1.50 [0.20; 24.00]	0.003	4.92 [0.47; 1,486.17]	7.79 [0.33; 1,486.17]	0.0237	-
C1INH: 25 j./kg [40-41]; h [IQR]	6.17 [0.33; 15.35]	15.35 [14.00; 22.83]	0.007	14.08 [3.00; 29.08]	26.00 [25.00; 50.83]	0.01	7,72 [3,89; 16,52]; p < 0,05

CI — confidence interval; IQR — interquartile range

assessment of the patients, whereas in the case of rhC1INH and icatibant, these parameters were defined based on the decreased size of oedema in a visual analogue scale (VAS).

It should be mentioned that the use of conestat alfa and its comparators is connected with the occurrence of some unique undesirable effects. In the case of conestat alfa, it is the risk of occurrence of allergic reaction to rabbit antigens present in trace amounts in the preparation [20]. There is some threat connected with the use of C1 esterase inhibitor concentrate because it is obtained from plasma, which may result in passing on viral infections [44, 45]; however, thus far such cases have not been proven [45]. However icatibant, which has an inhibitory effect on the production of bradykinin, may cause impaired vasodilatation, which consequently may influence the increase of blood pressure, and this fact may be of vital importance to patients with vascular diseases [43]. Furthermore, the use of all preparations is connected with the risk of occurrence of hypersensitive reaction to the product in the place of administration [20, 43, 44].

It should be also emphasized that the use of conestat alfa instead of plasma-derived C1 esterase inhibitor concentrate is important for people who refuse to take haematogenous drugs for religious reasons [2]. The next advantage of the use of conestat alfa is the possibility of its unlimited production compared to C1INH inhibitor made from human blood. Production of conestat alfa by using DNA recombination in the milk of transgenic rabbits increases the certainty of the drug's availability [2].

Additionally, according to the report of the CHMP (Committee for Medicinal Products for Human Use), the use of rhC1INH is safer in patients with capillary leak syndrome, and it does not increase the risk of side effects in the form of development of thrombosis, contrary to C1 esterase inhibitor concentrate [46].

The use of each of the above substances in the treatment of HAE attacks is connected with certain unique limitations and benefits. The choice of the best possible treatment should be based on individual preferences and medical contraindications for individual patients.

Conclusions

Based on the results of the systematic review presented in this paper, it may be stated that conestat alfa and its comparators (C1INH concentrate and icatibant) are effective in the treatment of acute HAE attacks. However, it is not possible to indicate the best therapeutic option due to the great heterogeneity (lack of homogeneity) of the gathered studies.

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