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Recombinant human C1 esterase inhibitor for acute hereditary angioedema attacks with upper airway involvement

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ABSTRACT

Background: Recombinant human C1 esterase inhibitor (rhC1-INH) is approved for treatment of hereditary angioedema (HAE) in adolescents and adults. HAE attacks that involve the upper airway can be life threatening, and data on the administration of rhC1-INH for these types of attacks are currently limited.

Objective: To evaluate the efficacy and safety of rhC1-INH for treatment of acute HAE attacks with upper airway involvement.

Methods: A pooled analysis of data from three clinical trials with open-label extensions examined rhC1-INH for treatment of acute HAE attacks with upper airway involvement. Patients with functional plasma C1 esterase inhibitor <50% of normal who had experienced an acute upper airway HAE attack and received rhC1-INH were identified retrospectively based on severity of breathing or swallowing symptoms. The primary end point was the time to beginning of relief (time at which the overall visual analog scale score [0–100 mm] decreased from baseline by ≥ 20 mm for two consecutive time points [persistence]).

Results: Of 683 acute HAE attacks treated with rhC1-INH, data for 45 attacks with upper airway involvement were included. The median time to the beginning of symptom relief was 67 minutes (95% confidence interval, 60–120 minutes) and did not differ by attack number or by baseline breathing or swallowing symptom severity. Most attacks (91.1%) achieved the beginning of relief within 4 hours of rhC1-INH treatment. All attacks resolved without the need for any additional medication, and no patients required intubation or tracheostomy. Treatment with rhC1-INH was well tolerated, with no adverse events reported in more than one patient (except HAE reported as an adverse event [$n = 2$]).

Conclusion: This pooled analysis of clinical trial data supports the efficacy of rhC1-INH for treatment of acute HAE attacks with upper airway involvement.

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Hereditary angioedema (HAE) is a genetic disorder that causes episodic and recurring edema.^{1,2} In the general population, HAE is a relatively rare but potentially life-threatening disease, with a prevalence

ranging from 1 in 30,000 to 1 in 80,000 individuals.² HAE has been linked to mutations within the C1 inhibitor gene that cause truncation or misfolding of the C1 esterase inhibitor (C1-INH) protein (type I HAE) or disrupt its normal functionality (type II HAE). The lack of available functioning C1-INH disinhibits multiple protease cascades, which thereby allows production of vasoactive mediators, *e.g.*, bradykinin.^{1,2}

HAE may elicit edema in multiple anatomic locations, including the genitourinary tract, abdomen, extremities (*e.g.*, hands, feet), and the oropharyngeal-laryngeal region.^{1,2} Acute laryngeal attacks account for ~1% of all HAE attacks³; however, they are considered

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and serves as a speaker for CSL Behring and Shire. M. Cicardi reports receiving a research grant from Shire and serving as a speaker or consultant for Alnylam, BioCryst, CSL Behring, Pharming, Shire, and Sobi. J. Harper is an employee of Pharming Healthcare Inc., and a former employee of Salix Pharmaceuticals. A. Relan is an employee of Pharming Healthcare Inc.

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Table 1 VAS score questions for orofacial-pharyngeal-laryngeal attacks

Question No.	Question	Best Symptom Descriptor (score, 0 mm)	Worst Symptom Descriptor (score, 100 mm)
1	How ill do you feel?	Not at all ill	Extremely ill
2	Do you have pain?	No pain	Extreme pain
3	Do you have any swelling?	No swelling	Extreme swelling
4	How easy is it to breathe?	No problems breathing	Very difficult breathing
5	Is your speech affected?	Not at all affected	Extremely affected/cannot speak at all
6	Do you have difficulty swallowing?	Not at all	Great difficulty
7	How severe are the angioedema symptoms now for this location?	No symptoms at all	Extremely disabling

VAS = Visual analog scale.

the most serious complication of HAE due to the potential for airway obstruction and asphyxiation.⁴ Laryngeal edema is associated with changes in voice (*e.g.*, hoarseness, aphonia), throat tightening, dysphagia, and the feeling of a lump within the throat.³ In the case of a fatal laryngeal attack, three phases with a range of progressively worsening symptoms have been described (*i.e.*, phase 1, lump in the throat, swallowing difficulties; phase 2, onset of dyspnea to loss of consciousness; phase 3, loss of consciousness and mortality), although some patients may not exhibit all three stages (*i.e.*, some patients present with dyspnea, effectively skipping phase 1).⁵ Progression of laryngeal attacks through these phases occurs quickly (*i.e.*, within 5 hours of symptom onset), and some patients may progress from phase 1 to phase 3 in <20 minutes.⁵ Because of the rapid progression of potentially life-threatening symptoms, laryngeal attacks require prompt intervention and effective medications with a rapid onset of action.

Ruconest (Pharming Technologies B.V., Leiden, the Netherlands) is a recombinant human C1-INH (rhC1-INH) administered for the treatment of acute HAE attacks. Unlike human plasma-derived C1-INH, rhC1-INH is purified from the milk of transgenic rabbits and, therefore, lessens the risk of blood-borne infection and supply concerns associated with plasma-derived C1-INH.⁶ In multiple randomized controlled trials (RCT) that contained open-label extension (OLE) phases, rhC1-INH decreased the time to beginning of symptom relief in HAE attacks overall.^{6–10} Given the seriousness of upper airway attacks, this pooled *post hoc* analysis of phase 3 data assessed the efficacy and safety of rhC1-INH for treatment of acute HAE attacks that involve the upper airway (*e.g.*, pharyngeal or laryngeal attacks).

METHODS

Data from three independently conducted trials (NCT00225147 [C1–1205], NCT00262301 [C1–1304],

and NCT01188564 [C1–1310]) were pooled. Each RCT trial had an OLE phase to allow repeated treatment of patients with recurrent attacks. Data on attacks with upper airway involvement that were treated with rhC1-INH were identified retrospectively. Attacks with a ≥ 50 -mm score for breathing (question 4) or swallowing (question 6) before treatment on the orofacial-pharyngeal-laryngeal-specific visual analog scale (VAS) (Table 1) were included in this pooled analysis.

Details of the study design and patient population for the phase 3 trials were previously described.^{6,8–10} All study protocols were approved by an institutional review board and/or an independent ethics committee at each site. All the patients provided written informed consent. All the trials included patients ≥ 12 years of age (≥ 16 years of age for study C1–1304 and ≥ 13 years for study C1–1310) who had plasma concentrations of functional C1-INH < 50% of normal and who had experienced an eligible acute HAE attack. Attacks were eligible if (1) the attack occurred in the abdominal region, genitourinary region, orofacial-pharyngeal-laryngeal region, or peripheral sites (extremities); (2) the patient presented to the clinic within 5 hours of the onset of the attack; (3) the symptoms at the attack location had an overall severity score of ≥ 50 mm on the VAS; and (4) there was not a decrease in overall VAS score of ≥ 20 mm from the time of evaluation to just before dosing. Patients who presented with life-threatening symptoms received immediate treatment and were not randomly assigned to treatment in the RCT phases but could be treated with a study drug if they participated in the OLE phases.

In the RCT periods of the three studies, the patients received rhC1-INH or placebo (saline solution). The patients who completed the RCT portion of the study in which they were originally enrolled (studies C1–1205, C1–1304, and C1–1310) and new patients who met criteria for the RCT (studies C1–1304 and C1–1205)

could be enrolled in the OLE phases once the particular study's RCT phase was completed. During the OLE phases, the patients could receive additional doses of rhC1-INH as deemed clinically indicated by the investigator up to a maximum dose of 100 IU/kg in a 24-hour period.

Study Assessments and End Points

Symptom severity was assessed in all the studies by using the validated VAS. Overall symptom VAS scores were completed for each anatomic location involved. The primary end point was the time to beginning of relief, defined as the first time at which the overall VAS severity score decreased from baseline by ≥ 20 mm for two consecutive time points (persistence). The secondary end point was the time to minimal symptoms, defined as the time point at which the overall VAS score was < 20 mm. Additional end points included the following: time to beginning of relief and time to minimal symptoms for attacks associated with at least moderate breathing difficulty (*i.e.*, severity of ≥ 50 mm on question 4 [Table 1]), time to beginning of relief and time to minimal symptoms for attacks associated with at least moderate swallowing difficulty (*i.e.*, severity of ≥ 50 mm on question 6 [Table 1]), and the number of additional doses required during the OLE phases. Safety assessments included adverse event (AE) monitoring, clinical laboratory and immunogenicity testing, electrocardiogram, vital signs measurements, and physical examination. AEs were recorded through 3 days after the end of an HAE attack. All data were summarized by using descriptive statistics.

RESULTS

Of 683 acute HAE attacks treated with rhC1-INH ($N = 191$ patients) during the randomized controlled or open-label studies, 45 eligible attacks with upper airway involvement ($n = 34$ patients) were identified. Most of the 34 patients with upper airway attacks (Table 2) received rhC1-INH treatment for a single attack with upper airway involvement (82.4% [$n = 28$]). In addition, four patients were treated for two attacks, one patient for three attacks, and one patient received treatment for six upper airway attacks. Most of the 45 attacks with upper airway involvement (93.3%) were reported during the OLE phases. For the 22 attacks treated with an initial dose of 50 IU/kg, 18 (81.8%) required only a single dose of rhC1-INH. Administration of a second dose was more frequent (10/20 [50.0%]) among the patients who received a non-weight-based dose (2100 IU) for initial rhC1-INH infusion. Overall, the mean total dose of rhC1-INH that was required per attack was 53.4 IU/kg.

The median time to the beginning of symptom relief for all 45 attacks with upper airway involvement was

Table 2 Demographics and baseline disease characteristics for patients with upper airway attacks

Parameter	Patients ($n = 34$)
Age, mean (range), y	42 (16–70)
Sex, no. (%)	
Male	9 (26.5)
Female	25 (73.5)
Race, no. (%)	
White	30 (88.2)
Black	4 (11.8)
Treated attacks, no. (%)	
1	28 (82.4)
2	4 (11.8)
3	1 (2.9)
≥ 4	1 (2.9)
Total dose of rhC1-INH received per attack, mean IU/kg (range)*	53.4 (22–100)
Trial phase of rhC1-INH administered, no. (%)*	
OLE	42 (93.3)
RCT	3 (6.7)
VAS score, mean (range)*	
Baseline swallowing	71.8 (33–100)
Baseline breathing	35.4 (0–94)

rhC1-INH = Recombinant human C1 esterase inhibitor; OLE = open-label extension; RCT = randomized controlled trial; VAS = visual analog scale.

** $n = 45$ attacks with upper airway involvement.*

67.0 minutes (95% confidence interval, 60–120 minutes) (Table 3). The median time to achieve the beginning of symptom relief was similar between the first upper airway attack treated with rhC1-INH (91.5 minutes) and subsequent upper airway attacks (63.5 minutes). The median time to achieve the beginning of symptom relief with rhC1-INH treatment also was generally similar for upper airway attacks with at least moderate severity in baseline breathing difficulty or baseline swallowing difficulty (Table 3). Overall, median time to minimal symptoms was 272.5 minutes (95% confidence interval, 240–738 minutes). These data were similar to those for first upper airway attacks and attacks with at least a moderate severity of breathing or swallowing difficulty (Table 3).

Importantly, 41 of the 45 upper airway attacks (91.1%) achieved the beginning of relief within 4 hours of rhC1-INH treatment. In the remaining four upper airway attacks, the time to achieving this end point ranged from ~ 8 hours (range, 465–481 minutes) ($n = 3$ attacks) to 12 hours (719 minutes) ($n = 1$ attack). Three of these four attacks occurred in the patients who had

Table 3 Efficacy of rhC1-INH for treatment of acute HAE attacks with upper airway involvement

Type of Attack	Attacks, no.	Median Time to Beginning of Relief, min (95% CI)	Median Time to Minimal Symptoms, min (95% CI)
Any upper airway attack (<i>n</i> = 34)	45	67.0 (60–120)	272.5 (240–738)
First upper airway attack (<i>n</i> = 32)	32*	91.5 (62–120)	243.0 (240–728)
Subsequent upper airway attacks (<i>n</i> = 5)	10*	63.5 (37–481)	900.0 (240–NE)
Upper airway attack with baseline breathing VAS score of ≥ 50 mm (<i>n</i> = 12)	15	105.0 (67–125)	327.0 (240–NE)
Upper airway attack with baseline swallowing VAS score of ≥ 50 mm (<i>n</i> = 34)	44	66.0 (60–120)	245.0 (240–738)

rhC1-INH = Recombinant human C1 esterase inhibitor; HAE = hereditary angioedema; CI = confidence interval; NE = not estimable; VAS = visual analog scale.

*Attacks that occurred during the open-label extension phase only because the number of attacks from the randomized controlled phase (*n* = 3) was not sufficient to allow this calculation.

experienced multiple attacks with upper airway involvement during the studies. Furthermore, all 45 upper airway attacks resolved without the need for any other additional medication, and no patients required intubation or tracheostomy.

Treatment with rhC1-INH was well tolerated. A total of 15 AEs was reported in nine patients (26.5%) (10 of 45 attacks [22.2%]). No AE was reported in more than one patient (except for HAE reported as an AE [*n* = 2]). One patient experienced an AE (moderate pharyngeal-laryngeal HAE attack) that was considered serious because the patient received rhC1-INH treatment in a hospital setting; the time to the beginning of symptom relief for this patient was 63 minutes. No other serious AEs were reported. No incidences of hypersensitivity or allergic reactions, neutralizing antibodies, thrombotic and/or thromboembolic events, or clinically meaningful changes in laboratory test results were reported.

DISCUSSION

In this pooled *post hoc* analysis of phase 3 data, HAE attacks with upper airway involvement responded rapidly to rhC1-INH, with a median time to beginning of symptom relief of 67.0 minutes and time to minimal symptoms of a median of 272.5 minutes. The median time to beginning of symptom relief of upper airway attacks treated with rhC1-INH in the current analysis was generally similar to that previously reported for any attack locations treated with rhC1-INH in the three trials (66–122 minutes with rhC1-INH in RCTs; and 37–120 minutes in OLE phases).^{6–10} In addition, the percentage of upper airway attacks with beginning of relief within 4 hours of rhC1-INH treatment (91.1%) was similar to previously reported data for all attack locations during the RCT phases of the C1-1205 and C1-1304 trials (93%).¹⁰ Also, similar to previous data

with rhC1-INH,^{6–8,10} few safety issues emerged. The consistency of the overall response and safety to rhC1-INH across multiple attack locations was encouraging, given the identical pathophysiology that underlies attacks at all anatomic sites. Although the dosing regimens varied slightly among the studies included, the mean total dose administered for all HAE attacks with upper airway involvement was 53.4 IU/kg, which is consistent with the approved, labeled dose in the United States and European Union (*i.e.*, 50 IU/kg; maximum, 4200 IU). Analysis of these data also indicated that a single dose of 50 IU/kg would be effective to treat most upper airway attacks, although an additional dose could be provided based on the clinical response.

Several clinical trials have evaluated the efficacy of various treatments for HAE attacks with upper airway involvement, but they differ in study design, inclusion, and outcome measures; these variations make it difficult to compare across trials. In addition, published data specifically reporting on efficacy for upper airway attacks are limited for some treatments (*e.g.*, icatibant and rhC1-INH). However, a 2016 descriptive comparison of clinical data by Bork *et al.*,¹¹ which relied on some unpublished government sources for data on efficacy for laryngeal attacks (*e.g.*, icatibant), reported that the percentage of attacks that achieved onset of relief within 4 hours was similar with plasma-derived C1-INH (77.4–100.0%), ecallantide (88%), and rhC1-INH (90.9% [unpublished data, which only reported on 33 laryngeal attacks]).¹¹ These data were consistent with the current analysis, in which 91.1% of the 45 attacks with upper airway involvement achieved onset of relief within 4 hours with rhC1-INH. The results from the current analysis are also consistent with a European treatment registry review of rhC1-INH-treated HAE attacks, which reported that 100% of la-

ryngeal attacks ($n = 9$) responded to rhC1-INH therapy within 4 hours of treatment.¹² Our findings also are consistent with postmarketing data from a Czech Republic national registry that included 21 laryngeal attacks.¹³

The current analysis included a large number of attacks with upper airway involvement (45 attacks in 34 patients) that presented with comparable symptoms (*i.e.*, met similar inclusion and exclusion criteria) and were treated by using standardized methodology. Attacks with upper airway involvement represented ~6.6% of the HAE attacks (45/683) in the clinical trials included here, which is higher than the prevalence of laryngeal attacks previously reported in a retrospective chart review of patients with HAE at an angioedema outpatient center (~1% of all presenting attacks).³ The higher prevalence in the current pooled analysis likely reflected the clinical seriousness of attacks with upper airway involvement because the patients were less likely to present for treatment for less serious attacks. Interpretation of the current study was hindered by the uncontrolled and retrospective study design. However, given the prevalence of upper airway attacks in the HAE population, a retrospective analysis of pooled data from multiple studies was necessary to provide a large enough population to allow statistically meaningful analyses. In addition, the uncontrolled study design was necessary because withholding adequate treatment of potentially life-threatening attacks would be unethical.

CONCLUSION

The current study has several strengths, including incorporation of pooled data from multiple trials, use of a validated questionnaire to determine response, and being the largest analysis of upper airway attacks treated with rhC1-INH published to date. However, interpretation of the results may be limited by the *post hoc* nature of the study; the majority of attacks analyzed herein occurred during the OLE phase and did not have a placebo-controlled arm for comparison. Although the number of attacks was relatively small, it was similar to that reported from studies of other acute HAE treatments (*e.g.*, plasma-derived C1-INH; $n = 48$).¹⁴ This pooled analysis of data from six clinical trials (three RCTs each with an OLE) supports the

efficacy of rhC1-INH for treatment of acute HAE attacks that involve the upper airway in adolescents and adults.

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