



Efficacy and safety of recombinant C1 inhibitor for the treatment of hereditary angioedema attacks: a North American open-label study

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ABSTRACT

Background: The efficacy of recombinant human C1 inhibitor (rhC1INH) for the treatment of patients with acute hereditary angioedema (HAE) attacks has been demonstrated in 2 randomized, double-blind, placebo-controlled studies.

Objective: To assess the safety and efficacy of rhC1INH for repeated treatment of acute attacks of HAE.

Methods: In this open-label extension study, patients with eligible HAE attacks were treated with an intravenous 50-U/kg dose of rhC1INH with an option for an additional dose of 50 U/kg based on clinical response. Time to beginning of relief was assessed by patients using a 100-mm visual analogue scale (VAS). Safety evaluation was based on the clinical laboratory results and adverse events.

Results: Sixty-two patients were treated for 168 attacks (range, 1–8 attacks per patient). A total of 90% of the attacks were treated with a single 50-U/kg dose of rhC1INH. Median times to beginning of symptom relief for the first 5 attacks were 37 to 67 minutes. More than 90% of attacks responded within 4 hours after treatment with rhC1INH. There was no requirement for increased dosing with successive treatments. Thirty-nine patients (63%) reported at least 1 treatment-emergent adverse event, with most events rated mild to moderate. Seven severe treatment-emergent adverse events were reported, and all were considered to be unrelated to treatment with rhC1INH.

Conclusion: The results of this open-label extension support continued efficacy of rhC1INH after repeated treatments for subsequent HAE attacks. There was no increase in adverse event reporting after repeated exposure to rhC1INH.

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Introduction

Hereditary angioedema (HAE) due to C1 esterase inhibitor (C1INH) deficiency is a rare autosomal dominant disorder.¹ More than 200 causative mutations in the gene encoding C1INH have been described to date, with all resulting in a final common outcome of low functional C1INH levels in the plasma. The worldwide prevalence of HAE due to C1INH deficiency is unknown but estimated at approximately 1:50,000. HAE is clinically characterized by repeated, acute attacks of cutaneous, gastrointestinal, genitourinary, and oropharyngeal or laryngeal angioedema. These attacks are frequently painful and disabling and occasionally fatal because of airway involvement with asphyxiation. The clinical symptoms of HAE are highly variable among affected individuals, particularly with regard to the frequency and severity of angioedema attacks.

Some patients may experience attacks that require treatment as often as once every 3 days.^{1–3}

Understanding of the pathophysiology underlying HAE has led to the development of important therapeutic approaches. Deficiency of functional C1INH leads to dysregulation of the contact and complement systems,^{1,4} resulting in the generation of vasoactive peptides primarily via the contact system. Bradykinin, generated from plasma kallikrein interaction with high-molecular-weight kininogen, is widely accepted as the most important causative mediator of HAE attacks. Local bradykinin production results in increased vascular permeability and movement of intravascular fluid into the interstitial space, resulting in clinical symptoms of angioedema in a period of minutes to hours. Recognition of C1INH as the critical protein preventing such dysregulation of the contact system led to C1INH replacement as a rational strategy for the treatment of HAE. A number of controlled clinical studies have demonstrated the efficacy of on-demand C1INH replacement therapy in rapidly terminating acute HAE attacks.^{5–9}

Historically, plasma-derived C1INH concentrates have been used in the treatment of HAE. More recently, a recombinant human C1INH (rhC1INH) has been developed and studied for the treatment of acute HAE attacks. rhC1INH is isolated from the milk of transgenic rabbits and purified for human administration.¹⁰ Two double-blind randomized controlled trials (RCTs) have previously established the efficacy and safety profiles of rhC1INH for the short-term treatment of HAE.⁸ In these studies, rhC1INH dosed at 50 or 100 U/kg was found to be superior to placebo for the treatment of HAE attacks with regard to time to onset of symptom relief and time to minimal symptoms. No apparent efficacy differences were observed between the 50 and 100 U/kg doses of rhC1INH. The adverse event (AE) and immunosafety profile was favorable for both doses.

The objectives of the current study were to examine the efficacy, safety, and tolerability of repeated treatment with rhC1INH in individuals with HAE, given that such patients currently require lifelong treatment for recurrent angioedema attacks. We report results from the open-label extension (OLE) of the RCT.

Methods

Study Design and Patients

The OLE study of rhC1INH was an extension of the North American RCT (clinicaltrials.gov identifier: NCT00225147).⁸ The OLE phase was performed at 20 centers in the United States and Canada. All study activities were conducted in compliance with the Declaration of Helsinki and national regulations and approved by local institutional review boards.

Patient eligibility was determined by the inclusion and exclusion criteria in place for the double-blind study phase and reported in detail previously.⁸ Primary inclusion criteria were patients with HAE who were 12 years or older, functional C1INH less than 50% of normal, and written informed consent. Primary exclusion criteria were rabbit allergy with history of anaphylaxis or severe allergies or acquired C1INH deficiency. Qualified patients from the double-blind phase or newly enrolled patients were treated if they presented with an eligible HAE attack. Attacks were eligible for treatment with rhC1INH if meeting the following criteria: abdominal, facial-oropharyngeal, laryngeal, urogenital, and/or peripheral angioedema; less than 5 hours since symptom onset; overall severity score of 50 mm or higher on visual analogue scale (VAS) score for at least one eligible location; and no pretreatment improvement in overall severity score of 20 mm or greater on VAS.

Patients presenting with eligible HAE attacks were treated within 1 hour after attack eligibility was confirmed using 50 U/kg of rhC1INH administered by slow intravenous injection. An additional 50-U/kg dose could be administered at the investigators' discretion within 4 hours of the first dose as required. Patients were treated at

the study site and discharged after 4 hours or when minimal symptoms were achieved. Follow-up study visits were conducted at days 22 and 90. Patients experiencing further eligible HAE attacks could be treated repeatedly per study protocol for an unlimited number of episodes, although to complete the immunosafety evaluations, the required interval between treatments was 7 days.

Study Assessments and End Points

Treatment efficacy was assessed by patient report, using HAE-specific VAS instruments specifically developed for the rhC1INH clinical development program. Four instruments were used to assess the intensity of symptoms at specific anatomical locations: abdominal, oro-facial-pharyngeal-laryngeal, peripheral, and urogenital attack locations. For each location, a series of symptom-related priming questions were asked, and patients responded by marking an "X" on a 100-mm scale with descriptive anchors at each end. The final question for each anatomical location was the overall severity VAS item: "How severe are the angioedema symptoms now for this location?" (no symptoms at all to extremely disabling).

The VAS scores were recorded 1 hour before treatment, at the start of treatment, and after treatment at 0.25, 0.5, 1, 2, 4, 8, 12, 16, 24, and 48 hours. A study of 27 HAE patients has demonstrated the comprehensibility and relevance of the VAS items and their suitability for use in clinical trials of acute HAE.¹¹ Additional psychometric evaluation has found that a 20-mm change in the overall severity VAS indicates a minimal clinically important difference that could be used to define onset of relief (unpublished data).

The primary efficacy end point for the OLE phase was time to beginning of sustained relief of symptoms, defined as the time between rhC1INH administration and the first time point at which the overall severity VAS decreased by more than 20 mm compared with baseline for 2 consecutive VAS recordings for any eligible location. The secondary efficacy end point was time to minimal symptoms, defined as the time between rhC1INH administration and the time point at which the overall severity VAS score had decreased to less than 20 mm for all anatomical locations of an attack. Additional exploratory end points included percentage of patients with response (time to beginning of relief occurring within 4 hours), relapse, the development of new attack locations within 24 hours, and the use of any medication that may have interfered with assessment of the effect of efficacy of rhC1INH. Specifically, a location was assessed as having relapsed if, based on overall VAS score, beginning of relief of symptoms at the location occurred in less than or equal to 4 hours and within 24 hours was followed by an increase of VAS score up to at least the baseline score at any time point after the beginning of relief.

Safety assessments were conducted via collection of AEs recorded from treatment to day 90. Additional safety monitoring included data analysis of vital signs, electrocardiograms, physical examinations, and standard clinical laboratory parameters. Plasma samples were collected at screening, before treatment, and at days 22 and 90 for immunogenicity assessments. Immunogenicity studies included enzyme-linked immunosorbent assays (ELISAs) for IgM, IgG, and IgA antibodies against plasma-derived C1INH, rhC1INH, and host-related impurities (eg, rabbit milk proteins). Samples above the predefined ELISA cutoff levels were tested using confirmatory displacement assays.¹² Testing for anti-C1INH neutralizing antibodies was conducted on any samples above cutoff in the displacement or screening ELISAs.

Statistical Analyses

All patients receiving at least one dose of rhC1INH while enrolled in the OLE were included in the efficacy and safety evaluations. Because of the small number of patients treated for more than 5 attacks, statistical analyses were only performed on the first 5 attacks of the patients; all further attacks were described

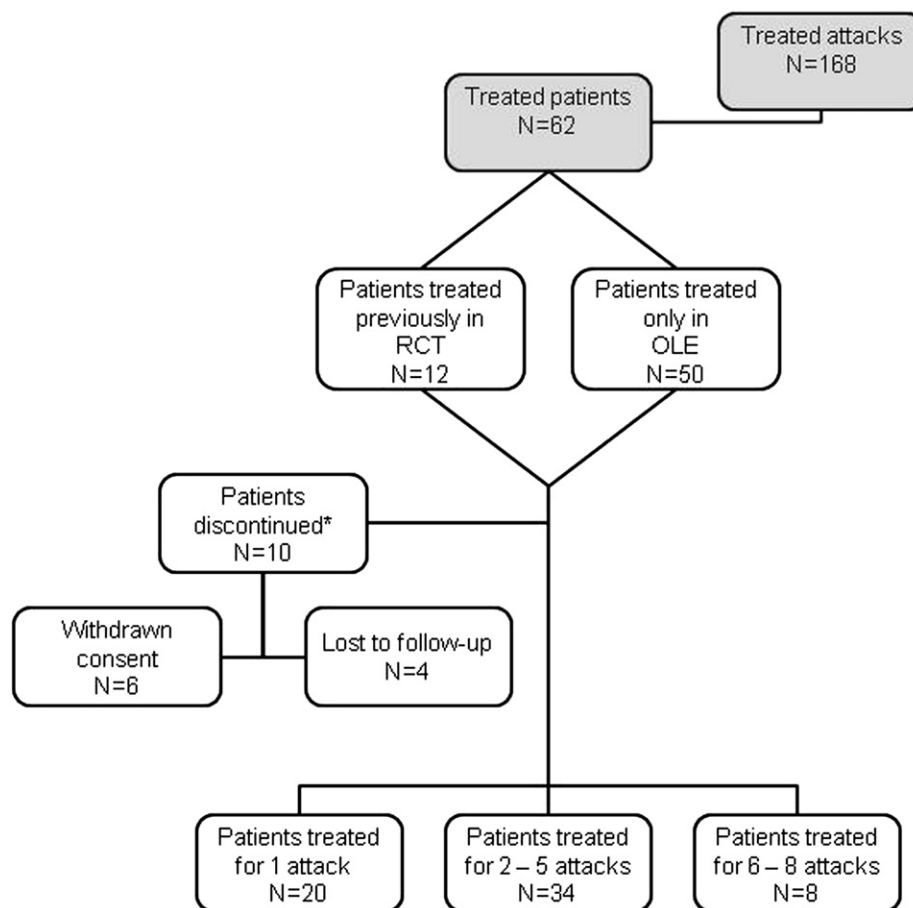


Figure 1. Patient disposition. Asterisk indicates 4 patients who withdrew their consent after being treated in the randomized controlled trial, 2 patients after receiving 2 treatments in the open-label extension (OLE). Four patients were lost to follow-up after being treated for 1 to 7 attacks during the 90-day follow-up period.

separately. If a patient was treated with rhC1INH in the double-blind phase, this was classified as attack 1 but was not included in OLE analysis to ensure validity of the immunogenicity evaluation. Primary and secondary end points are summarized as medians (95% confidence intervals [CIs]) and depicted as Kaplan-Meier plots.

Results

Patients

Sixty-two patients were treated for 168 HAE attacks during the OLE study performed from March 1, 2007, through January 20, 2010. Twelve patients were first treated with rhC1INH in the double-blind phase. Twenty patients were treated for 1 attack during the OLE, whereas 34 patients were treated for 2 to 5 attacks, and 8 patients were treated for 6 to 8 attacks. Ten patients discontinued the study (6 withdrew consent and 4 were lost to follow-up; none were due to an AE) (Fig 1). Baseline patient demographics are listed in Table 1.

The characteristics of eligible HAE attacks treated in the OLE are listed in Table 2. Notably, the mean overall severity VAS score at baseline was 74 to 83 mm. A total of 151 of 168 attacks (89.9%) treated with a single 50-U/kg dose of rhC1INH and no increase in additional-dose use was observed with subsequent treated attacks. Beyond attack 5, 13 of 15 attacks (86.7%) were treated with a single 50-U/kg dose of rhC1INH.

Efficacy

Median times to beginning of symptom relief for the first 5 attacks were 37 to 67 minutes. Figure 2 shows a Kaplan-Meier plot of time to

beginning of relief of symptoms for attacks 1 to 5. Median times to minimal symptoms for the first 5 attacks were 120 to 244 minutes.

The 95% CIs for the primary and secondary end points over successive treated attacks were overlapping. Response rates exceeded 90%, and no attack relapses were observed. Few patients took medications that may have interfered with efficacy assessments, most being analgesics taken on the day of the attack. No patient required treatment with any other HAE-specific therapy for the rhC1INH-treated attack. Only 1 patient developed a new attack location after treatment. Symptoms of the attack were minimal (VAS score, 9 mm).

Table 1
Patient baseline demographics

Demographic	Findings from all patients (N = 62)
Age, mean $\pm$ SD (range), y	33.3 $\pm$ 13.1 (13–61)
Sex, No. (%)	
Male	24 (39)
Female	38 (61)
Race, No. (%)	
White	54 (87)
African American	5 (8)
Hispanic	0 (0)
Asian	2 (3)
Other	1 (2)
BMI at screening, mean (range)	27.6 (19–44)
Patients with maintenance or prophylactic therapy, No. (%)	23 (37)

Table 2
Baseline characteristics of eligible attacks

Characteristic	Attack 1	Attack 2	Attack 3	Attack 4	Attack 5	Total
Patients, No.	50	42	26	20	15	62
Baseline VAS, mean $\pm$ SD	76.7 $\pm$ 13.8	74.1 $\pm$ 15.6	76.9 $\pm$ 14.6	79.6 $\pm$ 13.5	82.9 $\pm$ 12.1	
Anatomical locations of edema, No. (%)						
Abdominal	25 (50)	21 (50)	14 (56)	8 (40)	6 (40)	44 (71)
OFPL	10 (20)	13 (31)	3 (12)	4 (20)	3 (20)	20 (32)
Peripheral	16 (32)	9 (21)	12 (48)	7 (35)	8 (53)	32 (52)
Genitourinary	3 (6)	1 (2)	0	1 (5)	0	6 (10)
No. of attacks	50	42	26	20	15	168

Abbreviations: OFPL, oro-facial-pharyngeal-laryngeal; VAS, visual analogue scale.

A summary of the efficacy data for attacks 1 to 5 is presented in Table 3. Eight patients were treated for 15 attacks beyond attack 5 (attacks 6–8). These attacks responded with similar efficacy based on the primary and secondary end points as for attacks 1 to 5.

Safety

Headache and nasopharyngitis were the most frequently reported AEs. Most AEs were of mild or moderate severity. There were 20 serious AEs reported in 10 patients. Thirteen of these were HAE attacks reported in 8 patients. The other 7 serious AEs were reported in 4 patients, including severe vertigo in a patient 3 days after treatment, pneumonia the day after treatment, urosepsis occurring twice (6 days and 46 days after the second treated attack), and “itching of the lips and soft palate” shortly after treatment of the fourth treated attack in a patient. In the latter case, there were no reported urticarial lesions, rash, erythema, dyspnea, hypotension, or other systemic signs of an allergic reaction. The results of further evaluation, which included tryptase levels and testing for anti-rabbit dander IgE and anti-rhC1INH antibodies, were negative, suggesting the symptoms were part of an orofacial-pharyngeal HAE attack. The patient did not present with a subsequent HAE attack before the study closed.

Two patients had treatment-emergent anti-rhC1INH antibody results confirmed in the displacement assay. Both were IgM antibodies found at a single time point and not confirmed at subsequent time points, despite further rhC1INH treatments. These same 2 patients also had isolated, transient anti-host-related impurity antibodies at similar time points. Patients with anti-rhC1INH or anti-HRI antibodies did not report any treatment-related AEs, and there was no effect on efficacy observed. No neutralizing anti-C1INH antibodies were observed in any patient.

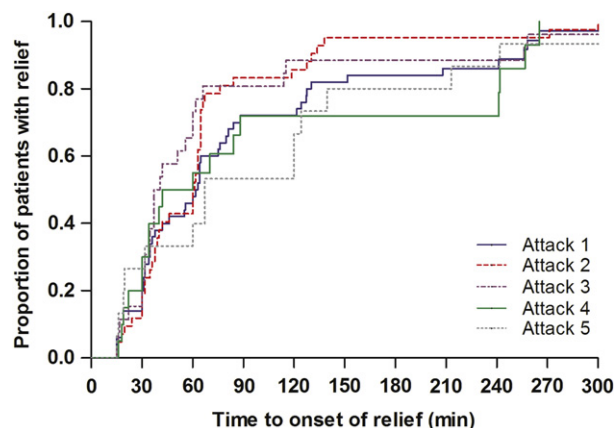


Figure 2. Kaplan-Meier plot of time to beginning of relief of symptoms for attacks 1 through 5.

Discussion

HAE is a rare genetic condition with repeated episodes of subcutaneous and submucosal swelling that can cause significant morbidity and mortality. rhC1INH is a novel therapy for HAE demonstrated by double-blind, controlled studies to be an effective and safe treatment for acute HAE attacks. The OLE phase data presented here support maintained efficacy and safety with repeated use in HAE treatment. Repeated treatment data demonstrated rapid onset of relief and high response rates. In addition, a favorable safety profile is found with no increase in AEs with repeated treatment. Consistent with reports on use of plasma-derived C1INH products, only sporadic antibodies were observed and not associated with any clinical hypersensitivity symptoms or reduction in efficacy.^{13,14} Few attacks were treated with a second dose, with most being oro-facial-pharyngeal-laryngeal attacks that likely reflect the clinical seriousness of these attacks. No trend for increasing dose use was observed with subsequent treated attacks.

This North American OLE safety and efficacy data for rhC1INH are consistent with European OLE data. In the European OLE study, HAE patients were treated with single vial of rhC1INH (2,100 U) with an investigator option of an additional 2,100-U dose as clinically required.¹⁵ Although dosing regimens were somewhat different, efficacy and safety results of the European OLE were similar, with somewhat higher response rates in this study, which could be related to the higher doses used. In addition, there was no loss of efficacy or increase in AEs over repeated treatments. Subgroup analysis of European OLE data revealed rhC1INH to be effective for attacks at different anatomical locations.¹⁵ Likewise, in the current OLE, efficacy of rhC1INH was demonstrated for repeated attacks at abdominal, peripheral, and/or oro-facial-pharyngeal-laryngeal locations.

The open-label study design and protocol used have both strengths and limitations. The patient population enrolled is comparable to that encountered in clinical practice with regard to demographics and angioedema attacks. Although patients with an increased risk of allergic reactions to the drug product were excluded, this is consistent with European labeling for rhC1INH, which specifies known or suspected rabbit allergy as a contraindication to treatment and indicates pretreatment testing for IgE antibodies against rabbit epithelium. To date, only one hypersensitivity reaction to rhC1INH has been reported, occurring in a healthy individual with rabbit allergy and high preexisting IgE against rabbit epithelium. A comprehensive analysis of immunosafety, which included antibody data from the current rhC1INH OLE study, has been reported.^{12,16}

Because HAE symptoms involving the airway or gastrointestinal tract are difficult for investigators to objectively quantify, HAE treatment studies have relied heavily on patient-reported outcomes. This approach is necessary to fully evaluate the nature and intensity of angioedema at all affected anatomical locations. Our OLE study used HAE-specific VAS instruments that have been

Table 3

Summary of efficacy data for attacks 1 to 5

	Attack 1 (n = 50)	Attack 2 (n = 42)	Attack 3 (n = 25)	Attack 4 (n = 20)	Attack 5 (n = 15)
Doses administered, No. (%)					
1 dose	45 (90)	39 (93)	24 (92)	19 (95)	11 (73)
2 doses	5 (10)	3 (7)	2 (8)	1 (5)	4 (27)
Median time to beginning of relief of symptoms (VAS decrease of 20 mm with persistence)					
Minimum (95% CI)	62.5 (38.0–76.0)	60.5 (39.0–65.0)	37.0 (33.0–60.0)	51.0 (30.0–114.0)	67.0 (30.0–124.0)
Median time to minimal symptoms (VAS score <20 mm for all locations)					
Minimum (95% CI)	145.0 (124.0–256.0)	228.0 (120.0–250.0)	120.0 (80.0–265.0)	242.5 (85.0–970.0)	244.0 (127.0–335.0)
Response rate (attacks with time to relief within 4 hours after baseline), %	94	98	100	90	93
Attacks with relapse (in patients with response, recurrence of symptoms within 24 hours), No.	0	0	0	0	0
Patient took medication that may have interfered with the assessment of the impact of rhC1INH, No.	3	2	0	0	0
New location within 24 hours in attacks with response	1	0	0	0	0

Abbreviations: CI, confidence interval; rhC1INH, recombinant human C1 inhibitor; VAS, visual analogue scale.

quantitatively and qualitatively validated, supporting the quality of the patient reported data.¹¹ Efficacy assessments were made at discrete time points, which is likely to explain the magnitude of interattack variation in median values for main efficacy end points. The 95% CIs overlapped, and there was no trend with increasing treatment numbers, indicating maintained efficacy of rhC1INH with repeated treatments.

The major limitation of any open-label study, including this OLE, is the lack of a control arm in such study designs. However, the OLE data are consistent with previously published rigorous RCTs of rhC1INH. Response rates in both the RCTs and OLE demonstrate a response rate consistently greater than 90% with rhC1INH therapy. This response rate is higher than those observed in trials of plasma-derived C1INH.^{5,6,9} Reasons for these differing response rates are not known but may be due to dosing differences among clinical studies. Importantly, these OLE data allow analysis of efficacy and safety with repeated therapy over time, in some ways replicating “real-world” treatment of HAE in a manner not possible using RCTs.

In conclusion, North American OLE study data indicate that rhC1INH is effective for the treatment of repeated angioedema attacks in HAE. Durable efficacy in conjunction with favorable tolerability and safety data over time provides substantial evidence supporting rhC1INH use in the acute treatment plans of HAE patients.

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