Original Article

Recombinant Human-C1 Inhibitor is Effective and Safe for Repeat Hereditary Angioedema Attacks

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What is already known about this topic? Randomized controlled trial results support the efficacy and tolerability of recombinant human C1 esterase inhibitor (rhC1INH) at 50 IU/kg for the treatment of acute hereditary angioedema attacks.

What does this article add to our knowledge?

- rhC1INH efficacy is maintained for the treatment of subsequent attacks.
- Single doses of rhC1INH are effective in most of the cases.
- Relapse rates were low.
- No increase in the number of adverse events or change in the adverse event profile was observed with rhC1INH treatments for repeat attacks.

How does this study affect current management guidelines? The present study supports the repeated use of rhC1INH for the treatment of recurring attacks in patients with hereditary angioedema.

BACKGROUND: Hereditary angioedema (HAE) caused by a deficiency in functional C1 esterase inhibitor (C1INH) is characterized by recurrent episodes of cutaneous and/or mucosal/submucosal tissue swelling affecting multiple anatomic locations. Previous studies demonstrated efficacy of recombinant human C1INH (rhC1INH) for acute HAE attacks.

OBJECTIVE: This study evaluated the efficacy and safety of rhC1INH (50 IU/kg) for the treatment of multiple HAE attacks in an open-label extension study.

METHODS: Time to onset of symptom relief and time to minimal symptoms were assessed using a Treatment Effect Questionnaire (TEQ), a visual analog scale, and a 6-point ordinal scale Investigator Score.

RESULTS: Forty-four patients received rhC1INH, and a single dose was administered for 215 of 224 (96%) attacks. Median time to beginning of symptom relief based on TEQ for the first 5 attacks was 75.0 (95% CI, 69-89) minutes, ranging from 62.5 (95% CI, 48-90) to 134.0 (95% CI, 32-119) minutes. Median time to minimal symptoms using TEQ for the first 3 attacks was 303.0 (95% CI, 211-367) minutes. rhC1INH was well tolerated. There were no discontinuations due to adverse events. No thrombotic or anaphylactic events were reported, and repeat rhC1INH treatments were not associated with neutralizing anti-C1INH antibodies.

CONCLUSIONS: A single 50-IU/kg dose rhC1INH was effective for improving symptoms of an HAE attack with sustained efficacy for treatment of subsequent attacks. rhC1INH had a positive safety profile throughout the study. This study supports repeated use of rhC1INH over time in patients with HAE attacks. **(J Allergy Clin Immunol Pract 2015;■:■-■)**

Key words: *Hereditary angioedema; Recombinant human C1 esterase inhibitor; Repeat attacks*

Hereditary angioedema (HAE), a rare genetic disorder, has a prevalence of around 1 in 50,000.[1] With deficiency of functional C1 esterase inhibitor (C1INH), overproduction of bradykinin results in increased vascular permeability and acute angioedema attacks. Attacks of HAE are episodic, which vary widely among patients. The extremities, face, and abdomen are the most commonly involved sites. Oropharyngeal-laryngeal swelling,

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Abbreviations used
C1INH- C1 Esterase inhibitor
HAE- Hereditary angioedema
HRI- Host-related impurities
IS- Investigator Score
OLE- Open-label extension
rhC1INH- Recombinant human C1 esterase inhibitor
pdC1INH- Purified human plasma–derived C1INH
RCT- Randomized controlled trial
TEQ- Treatment Effect Questionnaire
VAS- Visual analog scale

while less frequent, can be life-threatening. More than 50% of the patients with HAE have at least a episode of laryngeal swelling in their lifetime.[2] HAE is associated with significant health burden.[3,4] Current guidelines recommend that all patients with HAE have access to medicine for the treatment of acute attacks.[5,6]

C1INH replacement therapy is a logical approach to HAE management, and purified human plasma–derived C1INH (pdC1INH) products have been approved for either prevention or treatment of acute attacks.[7] However, these products carry a potential risk for transmission of human pathogenic viruses and prions, and have been associated with thrombotic events.[8] In addition, shortages of available donor plasma sources can limit production.

Recombinant human C1INH (rhC1INH) is an important alternative treatment option to pdC1INH products that can address potential risks associated with blood-derived pathogens. In addition, the transgenic rabbit platform ensures a reliable and scalable supply of a product with uniform quality.[9] The recombinant protein, with a sequence identical to that of human C1INH, is expressed in mammary glands of transgenic rabbits and purified from milk. Because rhC1INH retains the specificity of human pdC1INH toward its target proteases, the mode of action is identical. Differences in the glycosylation of rhC1INH and pdC1INH do not affect the specificity of rhC1INH to inhibit its target proteases.[10] Population pharmacokinetic modeling supports a dosing scheme of 50 IU/kg, which achieves C1INH levels above the lower level of the normal range (0.7 U/mL) in at least 94% of the patients.[11] These plasma levels are required to achieve complete inhibition of inflammatory cascades as demonstrated by continued C4 cleavage and higher C4 b/c concentrations at lower doses.[12]

Previous randomized controlled trials (RCTs) indicate that rhC1INH at 50 and 100 IU/kg is a highly effective and well-tolerated treatment for acute HAE attacks.[13] Furthermore, open-label extension (OLE) studies demonstrated that efficacy was maintained for subsequent acute HAE attacks.[14,15] For 119 patients treated for 362 attacks in these 2 studies, more than 80% of repeat attacks responded within 4 hours and most of the patients required only a single dose of rhC1INH. There was no increase in the incidence of adverse events or induction of neutralizing antibodies. The present pivotal study evaluated a dose of 50 IU/kg in a larger population of patients with HAE in an RCT followed by an OLE phase. Results of the RCT have been published separately.[16] This analysis focuses on the efficacy and safety of rhC1INH for repeated treatment of multiple attacks in the OLE phase.

METHODS

Study design

This study was the OLE portion of an international RCT (no. NCT01188564). In the OLE phase, patients were treated at 8 centers in the United States and 1 site each in Bulgaria, Israel, Italy, Macedonia, Poland, Romania, and Serbia. All study activities were conducted in compliance with the Declaration of Helsinki and approved by local institutional review boards.

The methods for the RCT of the study have been previously reported.[16] All patients who were treated in the randomized phase were eligible for participation in the OLE phase. All patients met the inclusion and exclusion criteria of the RCT study. They were 13 years or older at US sites and 18 years or older at other sites. Exclusion criteria included acquired C1INH deficiency and a medical history of rabbit allergy.

Patients who presented to a study center within 5 hours of the onset of an HAE attack were eligible to receive rhC1INH if their visual analog scale (VAS) overall severity score was 50 mm or more (0 mm = no symptoms; 100 mm = extremely disabling), with no evidence of spontaneous regression of angioedema symptoms between presentation to the clinic and infusion of study medication. For patients with multiple attack locations, the primary attack location was defined as the location with the highest overall VAS score at baseline.

Attacks were treated with 1 intravenous injection of rhC1INH at a dose of 50 IU/kg for patients weighing less than 84 kg or 4200 IU for patients weighing 84 kg or more. An additional dose was allowed 1 hour after initial dosing if warranted by the patients' clinical responses and at the discretion of the investigator. Patients remained under observation for up to 6 hours (see Figure 1 for full schedule of study assessments) and then were sent home with Treatment Effect Questionnaire (TEQ) and VAS forms to record the severity of symptoms at the 8, 12, and 24-hour time points and a diary to record the time at which there was complete resolution of symptoms. Adverse events and concomitant medications were also recorded. Phone calls were scheduled at approximately 24 hours and at day 4. Follow-up visits were planned for days 7, 28, and 90. The efficacy assessment forms and diary were collected at day 7.

Study endpoints

The severity of the angioedema attack was assessed by patients using the TEQ (see this article's Online Repository at www.jaci-inpractice.org for detailed questions) and the VAS and by physicians using a 6-point ordinal scale (Investigator Score [IS]) for each symptomatic anatomical location at 15-minute intervals for 2 hours, followed by 30-minute intervals through 6 hours.

The primary efficacy endpoint was the time to beginning of relief of symptoms at the primary attack location (based on questions 1 and 2 of the TEQ, with persistence of improvement maintained at the next assessment time). Time to onset of symptom relief was also assessed on the basis of VAS score decrease of 20 mm or more or IS score decrease by at least 1 point from baseline at the primary attack location. The *secondary efficacy endpoint* was the time to minimal symptoms at all affected locations for the first 3 attacks, and was defined as the time point at which patients responded with a "Yes" to question 3 of the TEQ. This was assessed only for the first 3 treated attacks because patients were typically discharged 2 hours after rhC1INH administration, and the endpoint usually was reached after this time. Time to minimal symptoms was also assessed using the VAS (VAS score <20 mm at all affected locations) and the IS (IS ≤ 1).

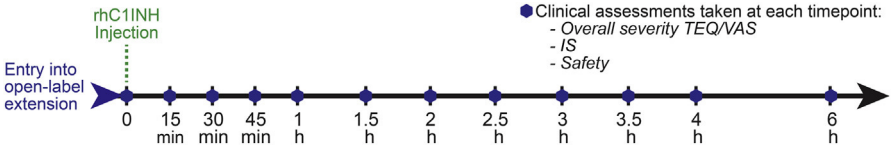

FIGURE 1. Schedule of assessments.

Data collected up to 24 hours from baseline for the first 3 attacks was assessed for the incidence of attacks occurring at new locations, or relapse of symptoms for locations with beginning of relief of symptoms at 4 hours or less according to responses to questions 1 and 2 of the TEQ.

Safety was monitored in all patients. Immunogenicity (IgM and IgG antibodies against rhC1INH, and antibodies against host-related impurities [HRI]) was tested on samples obtained at screening, before treatment, and at days 28 and 90. Antirabbit dander IgE was tested on samples collected at screening and at day 28 using a validated, commercially available system (ImmunoCAP, Phadia, Sweden; or equivalent). Predefined cutoff values in ELISA for anti-HRI and for anti-C1INH antibodies of IgM and IgG were more than 100%, more than 50%, and more than 15%, respectively. These cutoff levels were set on the basis of ELISA testing results (mean + 3 SD) for plasma samples from healthy volunteer subjects and patients with HAE who had never been treated with rhC1INH.

Statistical analyses

All patients received rhC1INH in the OLE phase were included in the safety analysis. All patients treated with rhC1INH in the OLE phase with any available efficacy data comprised the OLE intent-to-treat analysis set. For patients who received rhC1INH in the RCT phase (either as their randomized treatment or as open-label rescue medication), the first attack in the OLE phase was labeled as attack 2. For patients who received saline in the RCT phase, the first attack in the OLE phase was labeled as attack 1. All analysis data sets and outputs were produced using SAS (version 9.1 or higher).

Summary statistics including the number of patients, mean, and SD were presented as continuous variables. For categorical variables, the absolute counts (n) and percentages (%) of patients with data were presented per category. All percentages were presented to integer values. For time-to-event analyses, time to beginning of relief of symptoms, and time to minimal symptoms, the median time to event (with 95% CI) was presented for each attack and for all attacks, and Kaplan-Meier plots were presented for each attack only.

The cumulative number of patients with beginning of relief of symptoms at each time point was summarized using counts and percentages. TEQ results at each time point were summarized by attack using counts and percentages for the primary attack location. The overall VAS score was presented by attack number. The IS at each time point and the point change from baseline for all post-baseline time points were summarized as continuous variables and by counts and percentages and summarized by attack. The number of patients who received a second rhC1INH dose was summarized using counts and percentages by attack number.

RESULTS

Forty-four patients were treated for 224 HAE attacks in the OLE phase. Of the 44 patients, 24 (55%) had been randomized to receive rhC1INH and 20 (45%) had been randomized to the saline group during the RCT phase. Eight patients randomized to saline had received rhC1INH as rescue medication during the RCT phase. Thus, for 32 patients, the first OLE-phase HAE attack was labeled as attack 2, and for the remaining 12, the first OLE-phase attack was labeled as attack 1. Thirty-nine patients completed the study. Two patients withdrew consent, 1 discontinued for pregnancy, 1 discontinued as a result of moving, and 1 patient withdrew because of noncompliance.

TABLE I. Demographic and HAE attack characteristics

Characteristic	OLE intent-to-treat population (N = 44)
Age (y), mean ± SD	39.7 ± 14.4
Sex, n (%)	
Female	26 (59)
Male	18 (41)
BMI (kg/m^2), mean ± SD	28.7 ± 8.0
Weight (kg), mean ± SD	82.5 ± 23.1
Race, n (%)	
White	42 (95)
Black/African American	2 (5)
Ethnicity, n (%)	
Hispanic/Latino descent	1 (2)
Primary attack location, no. of attacks (%)	
Abdominal	101 (45)
Peripheral	92 (41)
Facial	18 (8)
Oropharyngeal-laryngeal	8 (4)
Urogenital	5 (2)
Total no. of attacks	224
Baseline VAS score (mm), mean ± SD	
Attack 1*	77.9 ± 13.8
Attack 2	78.6 ± 16.0
Attack 3	76.9 ± 14.1
Attack 4	76.4 ± 11.3
Attack 5	77.8 ± 13.8

BMI, Body mass index.
*Attack 1 from OLE phase only.

Baseline characteristics are summarized in Table I. Most of the patients were white (95%), and there was a higher proportion of female patients (26 of 44 [59%]) in the study. Table I presents the overall VAS scores at baseline for attacks 1 to 5 and the primary anatomical locations of individual attacks. The most common anatomical locations of the HAE attacks were abdominal (45%) and peripheral (41%) sites, similar to the real-world distribution of attacks reported by patients and physicians.[17,18]

A total of 215 of 224 attacks (96%) were treated with a single 50-IU/kg dose of rhC1INH, and no increase in dose was needed for treatments of repeat attacks.

TABLE II. Time to beginning of relief of symptoms at the primary attack location (with continued relief at subsequent assessment)

	Median time to beginning of relief (min) (95% CI)					
Endpoint	**Attack 1***	**Attack 2**	**Attack 3**	**Attack 4**	**Attack 5**	**All attacks**
Patients, n	11	36	28	23	18	44
TEQ (questions 1 and 2, with persistence)†	90.0 (33-212)	76.0 (60-105)	134.0 (75-150)	76.5 (58-150)	62.5 (48-90)	75.0 (69-89)
Patients, n	12	40	32	25	20	44
VAS score decrease ≥20 mm, with persistence	105.0 (100-211)	75.0 (60-90)	105.0 (62-148)	93.0 (74-120)	90.0 (40-120)	90.0 (77-100)
Patients, n	12	40	32	25	20	44
IS decrease ≥1 point	87.0 (60-90)	72.5 (45-88)	60.0 (60-90)	60.0 (45-90)	75.5 (34-105)	74.5 (60-76)

*Attack 1 from OLE phase only.
†The TEQ was not performed for 17 of the 224 total attacks.

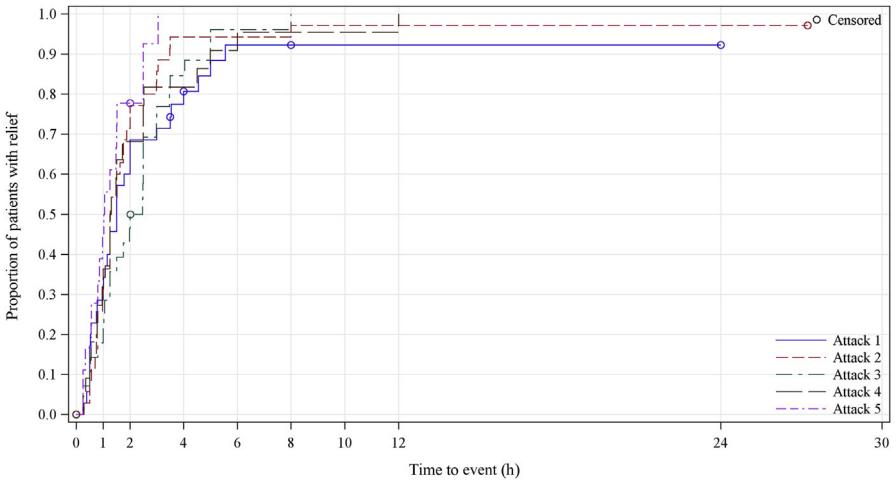

FIGURE 2. Kaplan-Meier plot of time to beginning of symptom relief (based on the treatment effect questions 1 and 2, with persistence) at the primary attack location—OLE ITT analysis set. *ITT,* intention to treat.

Efficacy

Table II summarizes the time to onset of symptom relief after rhC1INH treatment by attack number and for all attacks using the TEQ, VAS, and IS assessment instruments. Data are provided by attack number up to attack 5 because there were a limited number of patients with more than 5 treated attacks. Patients with more than 5 treated attacks are included in the "all attacks" column. The overall median time to relief of symptoms was 75.0 minutes (95% CI, 69.0-89.0) for all 5 attacks using the TEQ, and the median time to beginning of relief of symptoms for each of the first 5 attacks ranged from 62.5 to 134 minutes. Median times to beginning of relief of symptoms were similar when assessed using the VAS and the IS, and were 90.0 and 74.5 minutes, respectively.

Kaplan-Meier estimates for time to beginning of symptom relief are shown in Figure 2 based on the TEQ. Treatment with rhC1INH led to consistent onset of symptom relief for repeat attacks. Results were similar for the Kaplan-Meier estimates based on the VAS scores (data not shown).

The proportion of attacks with persistent relief at 4 hours after rhC1INH treatment is given for individual attacks 1 to 5 and for all attacks (n = 224) during the OLE phase of the study in Table III. TEQ assessment was performed for 207 of 224 attacks, and the overall response rate was 84% (174 of 207). The response rate was at least 75% for each of the first 5 attacks regardless of the assessment method used. Overall rates of response were 79% (177/224) and 87% (184/224) based on the VAS and IS assessments, respectively.

The times to minimal symptoms based on TEQ, VAS, and IS are given in Table IV for the first 3 attacks and overall. The overall median time was 303 minutes for all attacks based on the TEQ with a range of 211 to 367 minutes. Median times were similar across efficacy instruments and were 243 and 244 minutes for all attacks as assessed by VAS and IS instruments, respectively. Kaplan-Meier plots of time to minimal symptoms for the first 3 attacks are shown in Figure 3. Times to minimal symptoms were similar for repeat attacks. Kaplan-Meier results were similar based on VAS scores (data not shown).

For the first 3 attacks, no patient in the OLE phase had an attack at a new location within 24 hours of treatment. In addition, *relapse* (defined as symptoms initially improved within 4 hours, but recurred within 24 hours according to responses to questions 1 and 2 of the TEQ) was infrequent. None of the 39 patients with a response for the first attack during the OLE phase had a relapse, 2 of 33 (6%) had a relapse after the second attack, and 1 of 18 (6%) had a relapse after the third attack.

TABLE III. Proportion of attacks responding* to rhC1INH

	Attacks with response* to rhC1INH, n (%)					
Endpoint	**Attack 1†**	**Attack 2**	**Attack 3**	**Attack 4**	**Attack 5**	**Total attacks**
Attacks, n	11	36	28	23	18	207‡
TEQ (questions 1 and 2, with persistence)	9 (82)	33 (92)	24 (86)	18 (78)	17 (94)	174 (84)
Attacks, n	12	40	32	25	20	224
VAS score decrease ≥20 mm, with persistence	9 (75)	33 (83)	25 (78)	19 (76)	16 (80)	177 (79)
Attacks, n	12	40	32	25	20	224
IS decrease ≥1 point	11 (92)	38 (95)	29 (91)	25 (100)	17 (85)	194 (87)

*Response defined as beginning of relief by 4 h.
†Attack 1 from OLE phase only.
‡The TEQ was not performed for 17 of the 224 total attacks.

TABLE IV. Time to minimal symptoms at the primary attack location for the first 3 attacks and for all attacks

	Median time to minimal symptoms (min) (95% CI)			
Assessment	**Attack 1***	**Attack 2**	**Attack 3**	**All attacks**
Patients, n	11	36	21	44
TEQ (question 3)	243.0 (76-1440)	304.0 (150-719)	272.0 (210-480)	303.0 (211-367)
Patients, n	12	40	25	44
All VAS score <20 mm	290.0 (120-1440)	240.0 (120-300)	268.0 (181-480)	243.0 (150-272)
Patients, n	12	40	25	44
All IS ≤1 point	244.0 (117, -)	180.0 (120-301)	268.0 (181, -)	244.0 (181-300)

-, Not estimable.
*Attack 1 from OLE phase only.

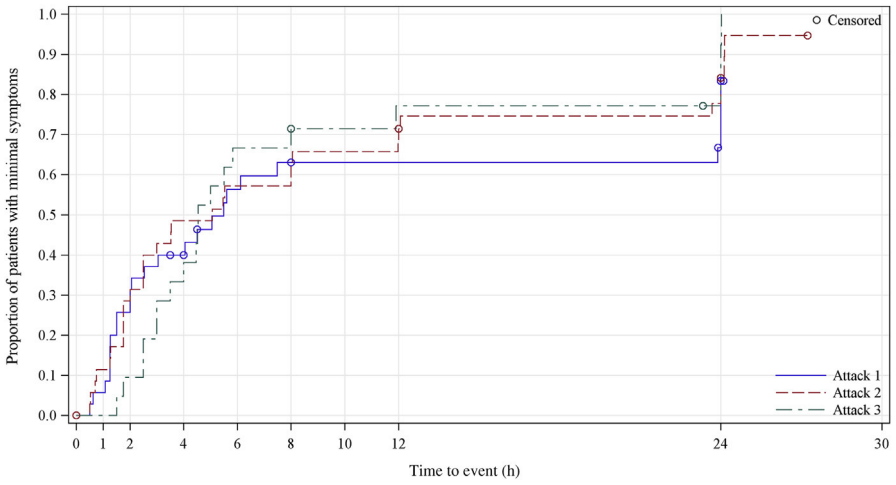

FIGURE 3. Kaplan-Meier plot of time to minimal symptoms (based on the treatment effect question 3) at the primary attack location—OLE ITT analysis set. *ITT,* Intention to treat.

Safety

Twelve of 44 patients (27%) reported treatment-emergent adverse events within 72 hours of completion of infusion that were mild or moderate in severity and similar to events reported during the RCT phase of the study.[16] No patient discontinued treatment because of an adverse event. Adverse events occurring in 2 or more (≥5%) patients within 72 hours of the completion of rhC1INH infusion were nasopharyngitis, elevated D-dimer concentration, headache, and cough. D-dimer concentrations were elevated at the time of an acute attack and generally decreased by day 7.

Fifteen mild or moderate adverse events in 4 patients were considered treatment-related: flatulence (4 events), diarrhea (3 events), increased lacrimation (2 events), back pain, chills, fatigue, nasopharyngitis, pruritus, and rash (1 event each).

Five patients had 9 severe treatment-emergent adverse events that resolved and were not considered to be related to study treatment: 1 patient with 3 events of abdominal pain, 1 patient with 2 events of headache and 1 event of vomiting, and 3 separate patients with a report of animal bite, facial HAE attack, or increased blood pressure. There was 1 serious event reported

of an HAE attack requiring hospitalization approximately 25 days after the administration of rhC1INH.

There was no increase in the frequency of adverse events with increasing numbers of rhC1INH administrations: following attack 1, 7 of 12 (58%) patients experienced adverse events compared with 16 of 40 (40%), 10 of 32 (31%), 8 of 25 (32%), and 8 of 20 (40%) patients following attacks 2, 3, 4, and 5, respectively. No pattern of emerging adverse events was observed for multiple attacks.

No neutralizing anti-C1INH antibodies were observed in any patient after repeat treatment with rhC1INH. Five patients had confirmed anti-rhC1INH antibodies of the IgG isotype. One patient had elevated IgG antibodies during attacks 2, 4, and 5, 1 during attacks 2, 13, and 15, 1 during attacks 3 to 17, 1 during attack 5 only, and 1 patient during attacks 13 and 14. Similar efficacy results were observed for each of these patients in the presence and absence of positive antibody results, suggesting no effect of antibodies on the efficacy of rhC1INH in treating acute angioedema attacks. Three patients experienced adverse events of rash, 2 of whom tested positive for HRI antibodies. No other patients reported any adverse event suggestive of a symptomatic hypersensitivity reaction. No anaphylactic reactions were observed in any patient, and there was no induction of IgE antibodies to rabbit dander epithelium.

There were no clinically relevant mean changes or shifts from baseline in hematology or biochemistry parameters or vital signs. No thrombotic events occurred in any patient during the study.

DISCUSSION

rhC1INH is a novel therapy for HAE that has been shown in RCTs to be an effective and safe treatment for acute HAE attacks. The present OLE-phase data demonstrate that rhC1INH provides persistent relief of symptoms for repeat HAE attacks in a large population of patients with HAE with diverse attack locations. Most of the attacks had onset of relief within 4 hours of rhC1INH treatment. Treatment with rhC1INH was well tolerated, and the incidence of symptom relapse was low for initial and subsequent attacks. Almost all attacks were treated with only a single dose of rhC1INH. There were no increases in adverse events, or additional dose requirements with treatments for multiple attacks. These results indicate that rhC1INH efficacy and safety are maintained when administered for repeated HAE attacks.

The study planned for the administration of a single rhC1INH dose of 50 IU/kg for each attack, with additional doses permitted as early as 1 hour after the completion of infusion of the first dose at the discretion of the investigator on the basis of assessment of the patient's response and symptoms. The vast majority (96%) of patients required only 1 dose of rhC1INH. Similarly, the relapse rate for patients in the OLE phase who responded to a single dose of rhC1INH was low, 0% after the first attack and 6% after the second or third attack. Relapse within 24 hours of treatment for patients responding to a single dose of rhC1INH has been low in all clinical trials to date.[13-16] In addition, the incidence of recurrence of symptoms after rhC1INH treatment was low. In an analysis of patients pooled from 2 RCTs and their OLEs, 93% (260 of 280) of the patients with attacks treated with rhC1INH remained free of recurrence or new attack symptoms within 3 days after treatment.[19]

The results of this study are consistent with those previously observed in RCTs reported by Zuraw et al[13] in which 95% of rhC1INH-treated patients (either 50 IU/kg or 100 IU/kg) experienced relief of symptoms within 4 hours with efficacy maintained for repeat attacks. Previous OLE studies also evaluated rhC1INH (50 IU/kg) treatment for repeated attacks.[14,15] In these open-label studies, efficacy (time to beginning of relief of symptoms) was consistent with that described in the present study (90 min vs 152 min for saline) and was comparable across multiple treated attacks. rhC1INH was well tolerated, with no increase in the incidence of adverse events on repeated treatment.

In contrast to these previous RCT and open-label studies, the present study (and the parent RCT[16]) used the TEQ-based efficacy assessment, which was used as the primary patient-reported efficacy assessment tool at the request of regulatory authorities. Patient-reported outcomes form the basis of efficacy tools used in HAE acute treatment studies because the goal of treatment is symptom relief rather than cure.[20] VAS instruments have been widely used in assessing HAE symptom severity, and content validity has been demonstrated.[21] Comparisons of results of the primary analysis using the TEQ in the present study with analysis using the VAS and with those of earlier studies using validated VAS instruments[13-15] show consistency across efficacy instruments. It is also important to note that investigator assessments of symptom relief using the IS were concordant with patient self-assessments of efficacy in the present study.

Treatment with rhC1INH for repeat HAE attacks was well tolerated, with a favorable overall safety profile. The most common events within 72 hours of the completion of infusion were mild or moderate headache, cough, nasopharyngitis, and increase in fibrin-D-dimer level. Fibrin D-dimer levels were elevated at presentation during an attack and before treatment with rhC1INH in almost all patients, and typically returned to normal levels within 7 days, reflecting no increased risk for thromboembolism after rhC1INH treatment. There was no increase in the percentage of patients with adverse events after treatment for repeat attacks, and the profile of adverse events was similar across attacks. There were no thrombotic events observed, and no anaphylactic reactions occurred. The incidences of antibodies to rhC1INH or HRI were low, with no impact on clinical efficacy or safety, confirming the absence of neutralizing antibodies. In an integrated analysis of immunogenicity findings from clinical trials, Hack et al[22] evaluated 155 patients treated with 424 doses of rhC1INH and reported that no patient developed neutralizing antibodies after repeated treatments.

There are several strengths to note regarding this study. Consistent with the patient population in clinical practice, the present study enrolled patients with HAE who were experiencing moderate to severe angioedema attacks across a real-world distribution of attack locations.[17,18] Inclusion of patients with any affected location is important given recent treatment guidelines advising early treatment of all attacks regardless of location or severity.[5,6] The present study also demonstrated good agreement across efficacy instruments, and the results analyzed using the TEQ were consistent with those observed using the validated VAS. In addition, investigator assessments of symptom relief were concordant with patient assessments. The study was limited, however, by the open-label design and lack of a control group, but efficacy results were consistent with those reported in RCT and other OLE studies of rhC1INH for acute HAE attacks.

CONCLUSIONS

A single 50-IU/kg dose of rhC1INH was effective in improving symptoms of repeat HAE attacks at all attack locations. rhC1INH had a positive safety profile. There was no increase or change in the adverse event profile with rhC1INH treatments for repeat attacks. rhC1INH treatment provided rapid and sustained symptom improvement with a low rate of symptom relapse. The present study supports repeated use of rhC1INH for the treatment of recurring attacks in patients with HAE.

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