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Abdominal Presentation of Acute Attacks of Hereditary Angioedema and Efficacy of Recombinant C1 Esterase Inhibitor in Symptom Resolution

H. Henry Li, MD, PhD[1]; Marc A. Riedl, MD, MS[2]; Jonathan A. Bernstein, MD[3]; Yun Hardiman, MS[4*]; Joseph Harper, PharmD[5]; and Anurag Relan, MD[5]

[1]Institute for Asthma and Allergy, P.C., Chevy Chase, Maryland; [2]University of California, San Diego, California; [3]University of Cincinnati, Ohio; [4]Salix Pharmaceuticals, Bridgewater, New Jersey; [5]Pharming Healthcare Inc., Bridgewater, New Jersey

*Former employee of Salix Pharmaceuticals.

ABSTRACT

Background: Hereditary angioedema (HAE), a rare disorder, can cause angioedema and pain in various parts of the body, including the abdomen.

Objective: This post hoc analysis evaluated the efficacy and safety of recombinant human C1 esterase inhibitor (rhC1-INH) for the treatment of acute abdominal HAE attacks.

Methods: Patients aged ≥13 years diagnosed with an acute HAE attack who received rhC1-INH or saline in a randomized, phase 3 study were eligible to receive repeat treatment with rhC1-INH in an open-label extension phase. End points included time to beginning of symptom relief of abdominal attacks (defined as decrease of ≥20 mm in overall visual analog scale [VAS] score from baseline to the onset of persistent beneficial effect), number of patients with the beginning of relief of symptoms at each scheduled time point, and overall and individual symptom (ie, abdominal pain, nausea) VAS scores. Safety assessments included adverse event monitoring.

Results: A total of 194 acute HAE attacks were experienced by 75 patients; 83 of these attacks (experienced by 26 patients) were abdominal attacks. Most abdominal attacks involved severe pain (97.6%) and severe nausea (69.5%). By 4 hours posttreatment with rhC1-INH, overall abdominal symptom intensity decreased from severe at baseline (mean VAS score, 83.2 mm) to mild (mean VAS score, 14.3 mm). The median time to symptom relief with rhC1-INH was approximately 1 hour and was generally consistent for up to 5 subsequent abdominal attacks. Treatment with rhC1-INH was well tolerated.

Conclusion: Repeat treatment of acute abdominal HAE attacks with rhC1-INH is efficacious and well tolerated.

INTRODUCTION

Hereditary angioedema (HAE) is a genetic disorder, estimated to affect 1 in 10,000 to 50,000 individuals, that is caused by a deficiency in functional C1 esterase inhibitor (C1-INH).[1,2] HAE is characterized by recurrent attacks of tissue edema affecting various anatomical locations, such as the periphery (eg, arms, legs), face, genitalia, larynx, and abdomen.[1,3] The duration of an HAE attack typically ranges between 1 and 4 days, with many patients experiencing at least 1 attack monthly.[2] Abdominal HAE attacks are common, accounting for approximately half of attacks in 1 study (57.1%).[4] Abdominal HAE attacks are characterized by pain that is considered severe by the majority of patients (87.0%).[5] However, other symptoms are reported in patients experiencing acute abdominal attacks, including nausea (87.0%), dizziness (87.0%), lightheadedness (87.0%), vomiting (82.6%), and diarrhea (69.6%).[5] Abdominal attacks may lead to partial or complete intestinal obstruction and ascites.[5] In the absence of an HAE diagnosis, patients experiencing abdominal attacks may undergo unnecessary tests or procedures, including exploratory surgery.[6,7]

The burden of HAE on patients cannot be overlooked, as the disorder can have a substantial negative impact on quality of life (QOL), medical costs, and work productivity. Patients with HAE have reported lower QOL compared with healthy individuals ($P < 0.0001$) or patients with allergies ($P < 0.05$).[4] Some HAE attacks may require emergency care.[8] One retrospective study reported that an estimated 41% of HAE-related emergency department (ED) visits resulted in hospitalization,[9] and a similar study noted that 53% of HAE-related admissions came through the ED.[10] Average length of hospital stay for a patient with an HAE attack has been reported to be approximately 5 days, with mean hospital charges of $22,728 (assessment period, 2004-2007) during the entire hospital stay. Whereas most of these patients are discharged to their homes, some (15.9%) may require home health care or care at a skilled nursing facility.[10] Employment may be impacted in patients with HAE (56%), as some HAE attacks require patients to take a leave from work, sometimes for several days.[11]

Recombinant human C1-INH (rhC1-INH) is indicated for the treatment of acute HAE attacks in adolescents and adults. Data from randomized clinical trials have shown that the median time to onset of symptom relief was significantly shorter with rhC1-INH 50 IU/kg and 100 IU/kg versus placebo (122 and 66 min, respectively, vs 495 min; $P = 0.01$ and $P < 0.001$, respectively).[12] Furthermore, the time to onset of sustained symptom relief was significantly shorter with rhC1-INH treatment compared with placebo (90 min vs 152 min; $P = 0.03$).[13] The overall median time to onset of symptom relief for patients receiving treatment with rhC1-INH for multiple acute HAE attacks (ie, up to 5 attacks total) was 75 minutes (range per attack, 62-134 min).[14] Because attacks in the abdomen are common and often disabling, this post hoc analysis further examined the efficacy and safety of rhC1-INH treatment for these attacks.

METHODS

Patients and Study Design

A post hoc analysis of data from the open-label extension phase of a phase 3, multicenter, randomized, controlled study (ClinicalTrials.gov identifier NCT01188564) was conducted. Details on the inclusion and exclusion criteria and patient population for the randomized, controlled study and open-label phase have previously been reported.[13,14] Briefly, patients aged ≥13 years and diagnosed with an acute severe HAE attack (ie, symptom onset <5 hours before evaluation, baseline visual analog scale [VAS] score ≥50 mm [severe]) were randomly assigned to receive a single intravenous injection of rhC1-INH 50 IU/kg (for patients with body weight <84 kg) or 4200 IU (for patients ≥84 kg), or saline. Patients who received treatment (rhC1-INH or saline) in the randomized, controlled phase of the study were eligible for inclusion in the open-label phase. In the open-label phase, attacks were also treated with rhC1-INH 50 IU/kg for patients <84 kg or 4200 IU for patients ≥84 kg.

Assessments

A VAS scale (range 0 mm [no symptoms] to 100 mm [extremely disabling)] was employed to evaluate time to symptom relief and symptom intensity. An HAE-specific VAS instrument with questions relevant to the anatomical location of symptoms (eg, abdominal symptoms) was completed by patients at baseline and at 15-minute intervals for 2 hours, then every 30 minutes through 6 hours, and at 8, 12, and 24 hours following treatment. Assessments included time to beginning of symptom relief (defined as ≥20 mm decrease from baseline in overall VAS score, with persistence [2 consecutive time points]), number of patients achieving the beginning of symptom relief at each scheduled time point, overall VAS score, and individual symptom VAS scores for abdominal pain and nausea. Symptom intensity was classified by VAS score as minimal (<20 mm), moderate (≥20 mm and <50 mm), or severe (≥50 mm).

Safety assessments included adverse event (AE) monitoring, clinical laboratory tests, vital signs, and physical examination. The presence of neutralizing anti–C1-INH antibodies was evaluated using an enzyme-linked immunosorbent assay. Patients were monitored for thrombotic and thromboembolic events during the study using Wells scores and ultrasound, if indicated.

HAE attacks were evaluated in all patients who were assigned to treatment in the randomized controlled trial and all patients treated with rhC1-INH in the open-label phase who had any available efficacy data. The safety population included any patients who received rhC1-INH.

For the analysis, the study included abdominal HAE attacks that were identified to be the primary attack location (defined as location with highest overall baseline VAS score if patients had multiple attack locations). Data were presented for up to 5 HAE attacks, to ensure a sufficient number of attacks were available for analysis. In the current post hoc analysis, the initial attack that received treatment with rhC1-INH (ie, either in the randomized, controlled phase or the open-label phase [for patients receiving saline in the randomized, controlled phase]) was considered the first attack. Summary statistics were presented for continuous variables (eg, number of patients, mean, standard deviation, median, 95% confidence interval). For categorical variables, counts and percentages of patients with data were presented. All statistical analyses were performed using 2-sided testing with a 0.05 level of significance.

RESULTS

A total of 75 patients who experienced 194 acute HAE attacks were included in the study. Of these patients, 26 (34.7%) presented with 83 (42.8%) abdominal HAE attacks (**Table 1**). Medical history indicated a mean of 13.2 abdominal attacks annually per patient. In the current study, all abdominal attacks were considered severe in intensity (mean VAS score, 83.2 mm), with the majority involving severe abdominal pain and severe nausea.

Treatment with rhC1-INH resulted in improvement (decrease from baseline) in overall VAS scores (**Figure 1**), with a mean decrease in intensity from 83.2 mm (severe) at baseline to 14.3 mm (mild) by 4 hours posttreatment. Improvements in mean overall VAS score persisted through 24 hours posttreatment (mean score, 4.2 mm). Furthermore, by 3 hours posttreatment with rhC1-INH, <10% of abdominal HAE attack symptoms were severe (ie, overall symptoms or individual symptoms of abdominal pain or nausea; **Figure 2**), and this effect continued through 24 hours postdose. Time to onset of symptom relief in 26 patients after an abdominal attack (n = 83 attacks) was rapid, with 50.0% experiencing symptom relief within 1 hour and 96.2% achieving symptom relief within 4 hours (**Figure 3**). All patients experienced symptom relief within 24 hours after receiving rhC1-INH treatment. The median time to symptom relief with rhC1-INH treatment was generally consistent (ie, approximately 1 hour) for subsequent acute abdominal HAE attacks (**Table 2**).

The majority of patients with abdominal HAE attacks experienced ≥1 AE following treatment with rhC1-INH (73.1%; **Table 3**). Most AEs were reported by 1 patient each. However, 6 AEs were reported by ≥1 patient receiving rhC1-INH: nasopharyngitis, increased fibrin D dimer level, HAE, dizziness, headache, and tooth abscess. The overall AE profile for rhC1-INH was maintained with repeat treatments for subsequent HAE attacks. No thrombotic or anaphylactic events or development of neutralizing antibodies occurred during rhC1-INH treatment for repeat attacks.

DISCUSSION

In the current study, acute abdominal HAE attacks were reported in 42.8% of total attacks, which was consistent with rates previously reported in the literature (range, 48% -57%).[4,15] The mean baseline VAS score indicated that abdominal HAE attacks included in the current analysis were severe in intensity, with abdominal pain and nausea reported by a majority of patients. Indeed, abdominal attacks have often been described by patients as extremely painful and are often experienced along with nausea and/or vomiting and diarrhea.[5]

Treatment with rhC1-INH improved symptoms of acute HAE abdominal attacks, with symptoms becoming mild in intensity and <10% of patients reporting severe symptoms by 3 hours posttreatment. The time to beginning of symptom relief remained generally consistent following treatment with rhC1-INH for subsequent acute abdominal attacks; these findings were consistent with efficacy data reported for rhC1-INH treatment of repeated HAE attacks in general (ie, occurring at any location).[14,16] Not unexpectedly, the tolerability profile for repeated rhC1-INH treatment of abdominal HAE attacks was also consistent with that of repeated treatment in acute HAE attacks in general.[14]

The characterization of acute abdominal HAE attacks in a clinically relevant population, namely patients with moderate to severe HAE attacks, is a strength of this study. Further characterization of acute abdominal HAE attacks not only supports the limited data available on this common site of HAE attacks,[5] but provides support for the administration of rhC1-INH to treat these potentially debilitating acute attacks. The efficacy of rhC1-INH for the treatment of multiple repeat HAE attacks has been previously reported[14,16,17]; however, the current analysis is

Table 1. Demographics and baseline disease characteristics

Characteristic	Patients (n = 26)
Mean age, y (SD)	40.2 (12.78)
Range, y	17-67
Female sex, n (%)	15 (57.7)
White race, n (%)	26 (100)
Mean annual HAE attacks, n (SD)	27.9 (27.89)
Mean annual abdominal HAE attacks, n (SD)	13.2 (14.21)
	Abdominal HAE attacks (n = 83)
Mean VAS score, mm (range)	83.2 (50-100)
Abdominal attack overall intensity, n (%)	
Minimal[a]	0
Moderate[b]	0
Severe[c]	83 (100)
Abdominal pain intensity, n (%)	
Minimal[a]	1 (1.2)
Moderate[b]	1 (1.2)
Severe[c]	81 (97.6)
Nausea intensity, n (%)	
Minimal[a]	11 (13.4)
Moderate[b]	14 (17.1)
Severe[c]	57 (69.5)

HAE, hereditary angioedema; SD, standard deviation; VAS, visual analog scale.
[a]VAS <20 mm.
[b]VAS ≥20 mm and <50 mm.
[c]VAS ≥50 mm.

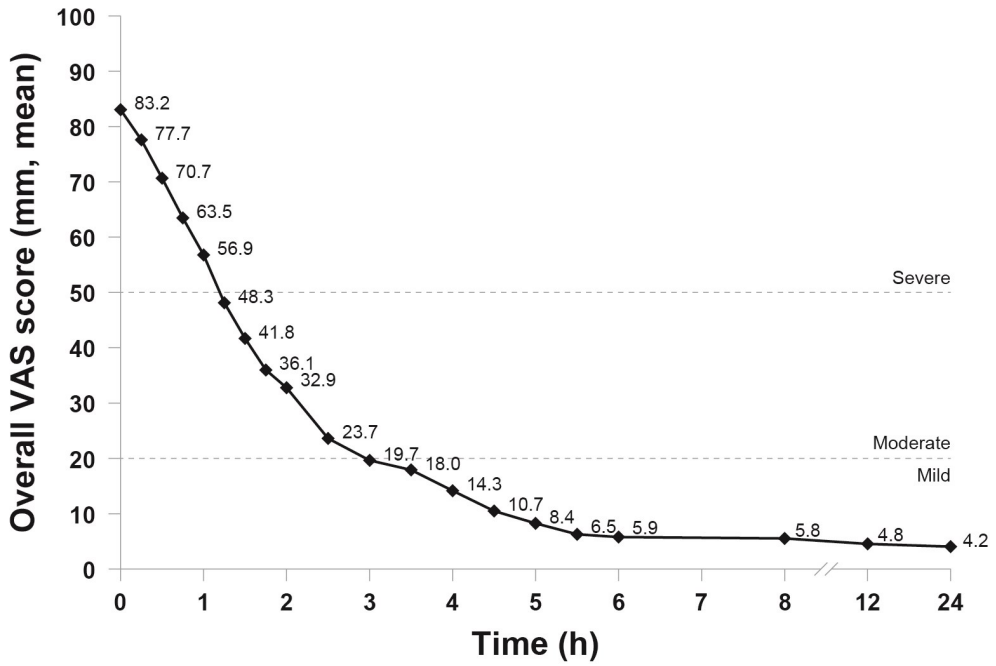

Figure 1. Overall VAS scores following treatment with rhC1-INH. Mean VAS scores rated as minimal (<20 mm), moderate (≥20 mm and <50 mm), and severe (≥50 mm).
rhC1-INH, recombinant human C1 esterase inhibitor; VAS, visual analog scale.

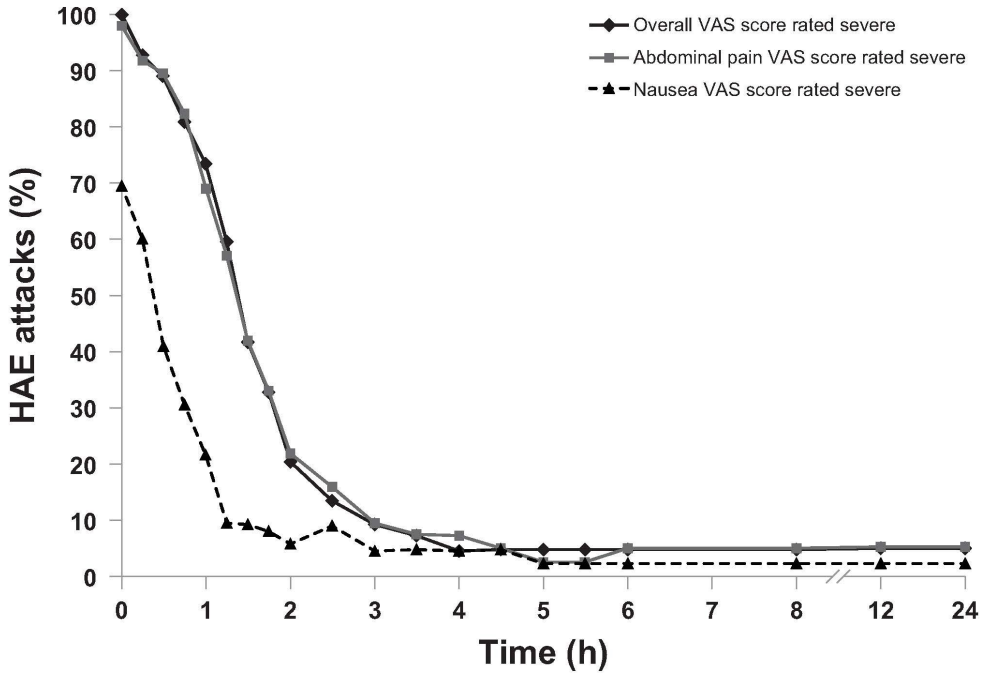

Figure 2. Percentage of symptoms of abdominal HAE attacks considered severe in intensity following treatment with rhC1-INH.
HAE, hereditary angioedema; rhC1-INH, recombinant human C1 esterase inhibitor; VAS, visual analog scale.

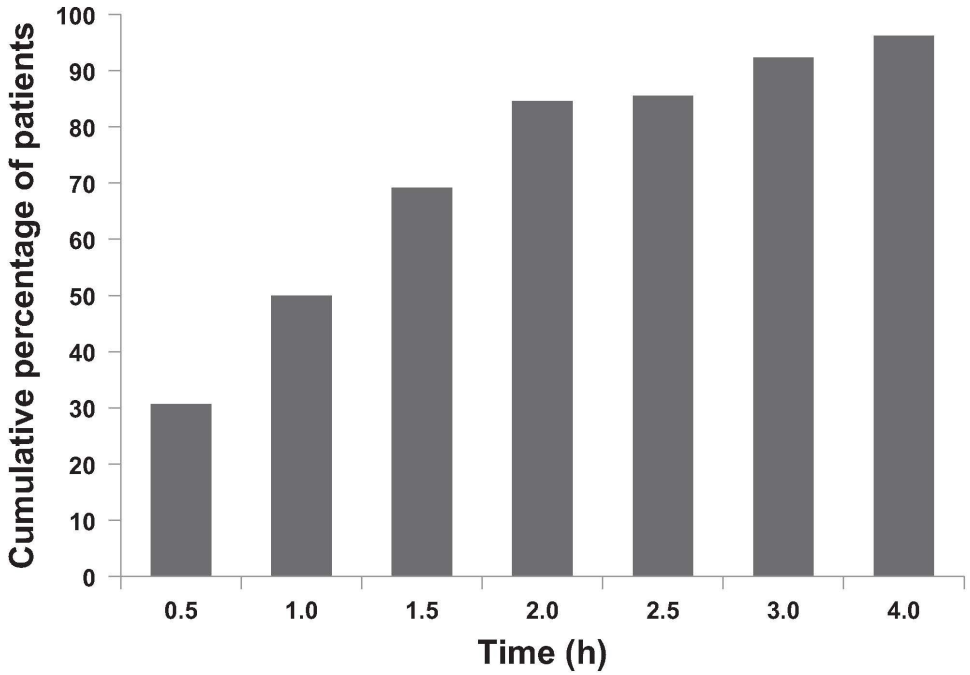

Figure 3. Percentage of patients experiencing abdominal HAE attacks with symptom relief after treatment with rhC1-INH.
HAE, hereditary angioedema; rhC1-INH, recombinant human C1 esterase inhibitor.

Table 2. Time to beginning of symptom relief following treatment with rhC1-INH for repeated abdominal HAE attacks

Time to beginning of symptom relief, minutes, median (95% CI)	Attack number					All attacks[a] (n = 26)
	1 (n = 14)	2 (n = 17)	3 (n = 12)	4 (n = 10)	5 (n = 8)	
	68 (30, 105)	60 (44, 75)	75 (62, 105)	84 (62, 107)	44 (35, 77)	62 (60, 77)

CI, confidence interval; HAE, hereditary angioedema; rhC1-INH, recombinant human C1 esterase inhibitor.
[a]Includes data from patients with >5 abdominal attacks.

Table 3. Adverse event summary[a]

Parameter	Patients, n (%)					
	Attack number					All attacks[b] (n = 26)
	1 (n = 6)	2 (n = 25)	3 (n = 20)	4 (n = 15)	5 (n = 12)	
≥1 AE	1 (16.7)	12 (48.0)	6 (30)	5 (33.3)	2 (16.7)	19 (73.1)
Discontinuations due to AE	0	0	0	0	0	0
Increased fibrin D dimer level	0	2 (8.0)	2 (10.0)	0	0	4 (15.4)
Nasopharyngitis	0	1 (4.0)	2 (10.0)	1 (6.7)	1 (8.3)	4 (15.4)
HAE	0	1 (4.0)	0	1 (6.7)	0	3 (11.5)
Dizziness	0	1 (4.0)	0	0	0	2 (7.7)
Headache	0	1 (4.0)	0	1 (6.7)	1 (8.3)	2 (7.7)
Tooth abscess	0	1 (4.0)	0	0	0	2 (7.7)

AE, adverse event; HAE, hereditary angioedema.
[a]AEs reported in >1 patient.
[b]Includes AEs for ≤13 HAE attacks.

novel in its examination of the efficacy and role of rhC1-INH in treatment of repeat acute abdominal attacks, particularly because patients experiencing abdominal HAE attacks may present to gastroenterologists with symptoms not readily identified as constituting an HAE attack.[18] Patients who have experienced abdominal HAE attacks may be misdiagnosed, sometimes for years, before HAE is recognized and treated with agents specifically designed to target the symptoms of an acute attack.[19,20] Although it is a rare disorder, gastroenterologists should consider HAE in the differential diagnosis of severe and recurrent acute abdominal pain and take into account a patient's family history, as well as prior episodes of acute angioedema in other anatomical locations. Various laboratory tests are currently available to establish a diagnosis of HAE, and patients may be referred to a health care provider with expertise in HAE for further care.

The results of the current analysis support that treatment with rhC1-INH is efficacious and associated with a positive clinical outcome in patients experiencing initial and subsequent acute abdominal HAE attacks, particularly given the rapid onset of symptom relief. Limitations of the study include the lack of a control group and a follow-up duration that was limited to 24 hours. In addition, no data are available regarding health-related QOL improvements, which would be valuable to examine in future prospective studies, given the burden of HAE on patients. In conclusion, this study supports the efficacy and safety of rhC1-INH for treatment of repeat acute abdominal HAE attacks.

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PREVIOUS PRESENTATION

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AUTHORSHIP

All authors analyzed data and wrote and edited the manuscript. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

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DISCLOSURES

H.H. Li reports receiving research grants from BioCryst, CSL Behring, Dyax, Pharming, and Shire; serving as a consultant for CSL Behring, Dyax, Salix Pharmaceuticals, Pharming, and Shire; and serving on the speakers' bureaus for CSL Behring and Shire.

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Y. Hardiman is a former employee of Salix Pharmaceuticals.

J. Harper is an employee of Pharming Healthcare Inc.

A. Relan is an employee of Pharming Healthcare Inc.

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ADDRESS CORRESPONDENCE TO:

H. Henry Li, MD, PhD

Institute for Asthma and Allergy, P.C.

2 Wisconsin Cir, Suite 250

Chevy Chase, Maryland 20815

Phone: 301-986-9262

Fax: 301-907-7910

E-mail: hl@allergyasthma.us