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Efficacy and safety of recombinant human C1-inhibitor for the treatment of attacks of hereditary angioedema: European open-label extension study

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Running head title: Efficacy and Safety of single dose rhC1INH in HAE

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Abstract

Background: Hereditary angioedema (HAE) due to C1 inhibitor deficiency is an autosomal dominant disorder, characterized by recurrent, potentially life-threatening, localized attacks of tissue swelling. Current treatment involves the infusion of C1 inhibitor protein (C1-INH) isolated from human plasma.

Objectives: This open-label extension to a European, Israeli and Argentinean randomized study (NCT00262301) aimed to investigate the efficacy and safety of recombinant human C1 inhibitor (rhC1-INH) as a first-line treatment following an HAE attack, together with its effect on subsequent attacks.

Methods: An HAE-specific visual analogue scale (VAS) 0–100 mm was used by patients to assess the severity of attack at four anatomical locations. Patients were treated with one, single-vial, fixed-dose of rhC1-INH (2100 U), followed by up to 2 further vials at the

investigators discretion. The primary endpoint was the time from first rhC1-INH injection to first onset of relief of symptoms (≥ 20 mm decrease on VAS). Response to treatment was defined as the onset of relief within 4 h.

Results: A total of 57 patients were treated for 194 HAE attacks. Overall, sustained relief of symptoms was achieved in 87% of rhC1-INH-treated patients within 4 hours of treatment, with 57% of attacks requiring only one vial of rhC1-INH. When categorized by successive attacks experienced by individual patients, the response rate to rhC1-INH treatment was 96%, 83%, 87%, 80% and 80% for attacks 1–5, respectively. Treatment with rhC1-INH was well tolerated, with no discontinuations due to treatment-emergent adverse events and no adverse events relating to immunogenicity.

Conclusions and clinical relevance: Treatment with rhC1-INH provides fast-onset relief for an HAE attack, with a high rate of therapeutic response maintained throughout subsequent attacks.

Keywords: Hereditary angioedema, recombinant human C1 inhibitor, single dose, open-label extension, NCT00262301

Introduction

Hereditary angioedema (HAE) due to C1 inhibitor deficiency is an autosomal dominant disorder characterized by recurrent attacks of tissue swelling. Deficiency of plasma C1 inhibitor protein (C1-INH) or the production of a dysfunctional enzyme, results in activation of the contact system (kinin cascade), complement and fibrinolytic systems and release of bradykinin which increases tissue vascular permeability [1, 2].

HAE attacks can affect many body organs. Abdominal mucosal edema can cause severe pain, mimicking a surgical 'acute abdomen', resulting in unnecessary operations. Attacks in the extremities can also be disabling, disfiguring and painful. Laryngeal attacks, albeit less frequent, are the most serious manifestation of HAE. They can lead to death by asphyxiation and are the primary cause of the high mortality rate associated with HAE [3].

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For decades, replacement therapy by intravenous infusion of C1-INH concentrate isolated from human plasma has been the standard of care for HAE attacks. This approach was shown by observational, as well as randomized, controlled trials to significantly shorten attack duration from a period of several days in untreated patients, to a few hours or less [4-8]. However, human blood products rely on donors, and carry a minimal, but never completely abatable, inherent risk of blood-borne infections.

A recombinant human C1 inhibitor (rhC1-INH; Ruconest[®], Pharming Technologies B.V., The Netherlands), extracted from the milk of transgenic rabbits to >99% purity [9], has recently demonstrated efficacy and safety in two randomized, controlled clinical trials [7]. Patients recruited to the European study received either 100 U/kg of rhC1-INH treatment or placebo during acute HAE attacks, whereas patients in the North American study received either 50 U/kg, or 100 U/kg or placebo. Both doses were highly effective in relieving the symptoms of HAE, reducing the severity and duration of attacks, and were well tolerated with no evidence for clinical relapse [7].

These studies evaluated the treatment of a single attack, while in 'real-life' HAE patients suffer from repeated attacks. Therefore, studying sequential treatments is expected to provide important data on potential production of inhibitory/sensitizing immune responses, as well as additional side effects that cannot be observed during a single treatment.

In this open-label extension (OLE) to the European randomized study, the safety and efficacy of rhC1-INH were evaluated for repeated attacks. In addition, the study evaluated "vial-based" dosing (i.e. doses of 1 vial [2100 U] administered as and when required), which was introduced to investigate perceived clinical practice preferences in Europe.

Material and Methods

Patients and assessment methods

The methodology of the randomized, double-blind, saline-controlled study (NCT00262301) has been previously reported [7]. All patients who were successfully screened for the randomized phase, as well as new patients who met the initial study criteria were eligible for participation in the OLE phase. Twenty-one centers in Argentina, Israel, Italy, Romania, Spain and the United Kingdom screened patients for this study (Table 1). Patients included in the study were ≥ 16 years of age who had a plasma C1-INH concentration $< 50\%$ of normal [10, 11]. Exclusion criteria included acquired C1-INH deficiency and a medical history of rabbit allergy.

The patients used HAE-specific visual analogue scales (VAS) to score the severity of their attacks at different anatomical locations (abdominal, urogenital, orofacial-pharyngeal-laryngeal, peripheral), with 0 mm representing 'no noticeable symptoms' and 100 mm representing 'extremely disabling' symptoms. A general VAS score assessed the overall severity of the HAE attack. The VAS used in this study have demonstrated comprehensibility and individual item relevance, as well as suitability for use in clinical trials of acute HAE [12]. The VAS scores were recorded at the time of first evaluation of the acute attack (1 hour before treatment initiation), immediately prior to initiation of treatment (time = 0) and at 0.25, 0.5, 1, 2 and 4 hours following treatment. Patients could then be discharged if they exhibited no or minimal symptoms. Additional VAS assessments were performed at 8, 12, 16, 24, and 48 hours, with once-daily assessments performed as necessary until symptoms were minimal.

The primary endpoint was the time from rhC1-INH injection to first onset of relief of symptoms, as defined by a ≥ 20 mm decrease from the initial VAS at any eligible anatomical location [12]. The secondary endpoint was the time from rhC1-INH injection to the time when 'minimal' symptoms occurred, defined as < 20 mm on the VAS for all anatomical locations. Exploratory endpoints included clinical response to treatment, defined as onset of relief

within 4 hours, and relapse, defined as a response followed by recurrence of HAE symptoms within 24 hours of treatment.

The study was conducted according to the ethical principles of the Declaration of Helsinki (2004) and all patients provided informed consent prior to screening. Appropriate Independent Ethics Committees approved the protocol, patient information sheet and informed consent form.

Study design

Eligible patients who presented with HAE attack symptoms within 5 hours of onset, who had an overall VAS severity score of at least 50 mm at one anatomical location, and who showed no evidence of spontaneous regression (VAS reduction ≥ 20 mm) after one hour, were treated with one vial of rhC1-INH (2100 U) by a slow intravenous injection. At the discretion of the investigator, up to two additional vials could be administered within 4 hours. Patients were discharged once they exhibited minimal or no symptoms. Efficacy assessments were conducted up to 48 hours. Safety assessments were performed at 24 hours, 22 days and 90 days following treatment. If a new attack had to be treated before completion of these follow-up visits, the follow-up visit schedule was reset accordingly.

Immunogenicity testing

Plasma samples were collected at time of screening, prior to treatment, and at Days 22 and 90 to test for antibodies. Initial antibody testing included the measurement of anti-C1INH antibodies (immunoglobulin classes IgM, IgG and IgA) against plasma-derived C1-INH and rhC1-INH. Testing for the presence antibodies against host-related impurities (HRI) was also performed. Cut-off levels of the assays were set using plasma samples from subjects with HAE naïve to rhC1INH. All above cut-off samples for anti-C1INH antibody or anti-HRI were analyzed in a confirmatory test, a displacement assay to determine whether or not increased values observed in the initial assay were due to specific or non-specific responses. Samples

confirmed in the anti-rhC1INH displacement assay as well as samples above cut-off in any of the three anti-pdC1INH antibody ELISAs were tested in a neutralizing anti-drug antibody (ADA) assay.

Statistical analyses

Efficacy analyses were performed on the modified intent to treat (mITT) population, defined as all patients who provided informed consent and received at least one dose of rhC1-INH during the OLE. Statistical analyses by attack number were performed on data recorded up to Attack 5; further attacks were described separately. Subgroup analyses were performed using the anatomical location of the attack. The safety analysis population was defined as all patients who received treatment during the OLE, with treatment-emergent adverse event (TEAE) data presented by absolute values and percentages, categorized by the number of HAE attacks experienced.

Results

A total of 57 patients were treated for 194 HAE attacks. Sixteen patients were treated with rhC1-INH for a single attack and 41 patients were treated for multiple attacks. Of the patients treated for multiple attacks, 34 were treated for 2–5 attacks and 7 patients for 6 or more attacks.

Baseline characteristics for the total study population are summarized in Table 2. A total of 31 (54.4%) patients were receiving maintenance therapy or prophylactic therapy at screening, predominantly androgens (n = 25), but also antifibrinolytics (n = 2), on-demand C1-INH concentrates before dental procedures/surgery (n = 2) and prophylaxis with plasma-derived C1-INH (n = 2).

Table 3 summarizes the overall VAS scores at baseline for Attacks No. 1–5 and in the total study population, the main anatomical locations of the individual attacks.

Treatment dose

Of the 194 treated attacks, 110 (57%) were treated with one vial (2100 U), 68 (35%) with two vials (4200 U), and 15 (8%) with three vials (6300 U); one patient was treated with five vials due to a protocol violation. Participants' body weight ranged from 43.8–120.0 kg, BMI from 19–40 kg/m² and the overall median dose of rhC1-INH was 34 U/kg. Patients treated with 3 vials tended to have a higher body weight (mean) than those treated with fewer vials. (Table 4) A greater percentage of abdominal and peripheral attacks were treated by a single 2100 U vial of rhC1-INH (74% and 64%, respectively) as compared with orofacial-pharyngeal-laryngeal attacks (28%). In attacks where an additional dose was provided, the median time at which the second dose was administered was 65 minutes (range: 5-250 minutes) after the first dose. The number of vials used to treat patients did not increase by attack number. From attacks 1-5, the numbers of patients treated with one vial were, respectively: 60%, 51%, 47%, 33%, and 50%.

Efficacy outcomes

Overall, rhC1-INH showed consistent efficacy on the primary endpoints for the first as well as the repeated treatment of HAE attacks. Median times to beginning of relief of symptoms for Attacks No. 1–5 were 60, 65, 120, 60, and 61 minutes, respectively. Median values for these endpoints varied around the discrete assessment time points and, the 95% confidence intervals overlapped considerably and Kaplan–Meier curves were similar for each number of attacks (Figures 1 and 2). Results for the response rates were similarly consistent and are shown by attack number in Figure 3. No clinical relapses were observed during the study.

Overall, rhC1-INH treatment provided sustained relief of angioedema symptoms within 4 hours of treatment in 169 out of 194 attacks (87.1%).

Primary and secondary outcomes by attack location are summarized in Table 5. Abdominal attacks exhibited the shortest time to relief and time to minimal symptoms following rhC1-INH treatment (median 0.5 hour and 4 hours, respectively), with orofacial-pharyngeal-laryngeal attacks taking approximately 2–3-fold longer to resolve.

The majority of attacks was treated with a single vial. The median time to the beginning of symptom relief for participants receiving 1 vial was 34.5, 120.0, 30.5, 60.0 and 61.0 minutes for Attacks 1–5 respectively. For patients receiving 2 or 3 vials, the median time to the beginning of symptom relief was 120.0, 62.5, 120.0, 90.0 and 60.0 minutes for Attacks 1–5 respectively. Two of the 84 attacks that received an additional dose (2.4%) had worsening VAS scores at the time of administration of the additional dose (both attacks failed to respond to initial treatment, one attack had worsened by the 2 h assessment and received an additional vial 3 hrs after initial treatment, the other attack had worsened by the 4 hr assessment and received an additional vial after 235 minutes after initial treatment).

Tolerability and safety assessments

Adverse events reported in more than in one patient with onset dates within 7 days after receiving rhC1-INH treatment are summarized in Table 6. Similar to previous studies of C1-INH treatments in HAE, most adverse events were mild to moderate in severity, with headache and nausea the most commonly reported. No serious adverse events were reported within 7 days of rhC1-INH treatment. No deaths or discontinuation of treatment occurred as a result of any TEAEs.

The occasional transient presence of anti-C1-INH and anti-HRI antibodies was not associated with clinical adverse events. No neutralizing antibodies were found. No relationship between anti-C1-INH antibody presence and rhC1-INH efficacy was noted (Table 7)

Discussion

Overall, rhC1-INH provided sustained relief of symptoms within 4 hours in 87% of the cases and was well tolerated without any clinical relapses. These study results also demonstrated the efficacy of rhC1-INH for the treatment of acute HAE attacks, irrespective of attack site (abdominal, genitourinary, orofacial/pharyngeal/laryngeal or peripheral). These findings are consistent with those previously observed in randomized, controlled, double-blind trials reported by Zuraw *et al.* [7], in which 95% of rhC1-INH treated patients (50 U/kg and 100 U/kg) experienced relief within 4 hours. In this study, the efficacy of rhC1-INH for the treatment of repeated acute HAE attacks was maintained throughout repeated treatment. In addition, rhC1-INH was well tolerated, with no increase in the incidence of adverse events on repeated treatments and no adverse events reported relating to immunogenicity.

This study investigated a convenient, single-vial fixed-dose of rhC1-INH (2100 U), with the option of an additional one or two vials. This dose corresponds to 30 U/kg for a 70 kg patient. In more than half of attacks one vial was used for the treatment of the HAE attack. Studies of human plasma-derived C1-INH products have previously demonstrated efficacy with doses of 20 U/kg, but not with 10 U/kg [5]. Combined with the data observed in the rhC1-INH controlled studies, these data suggests a dose–response relationship for rhC1-INH with an optimal efficacy at 50 U/kg [15].

This study allowed administration of 1 to 3 vials at the investigator's discretion. There seems to have been a preference to treat patients with higher body weights and patients with orofacial/ pharyngeal/ laryngeal attacks with higher doses (more than one vial). The latter presumably relates to the seriousness of these attacks. Dose increases often occurred before the effects of the initial dose could have been expected: approximately half of the additional doses were administered within the first hour, whereas the median time to onset of relief observed in the controlled studies was approximately 1 hour. Notably, only 2 of the 84 attacks that received an additional dose (2.4%) had worsening VAS scores at the time of

administration of the additional dose. Since attacks were not randomized to the various dose groups, no conclusions can be drawn from this study on whether the second dose was actually beneficial.

Kaplan–Meier plots of the primary and secondary endpoints and response rates show consistent results irrespective of the number of attacks. Variations in the median data for these endpoints must be interpreted in the context of the infrequent and discrete assessment time points, particularly around the median value. Assessment in smaller time increments may help to address this issue in future studies.

This study confirms that rhC1-INH is highly effective in resolving angioedema attacks involving all anatomical locations. The variations in time to onset of relief and time to minimal symptoms between locations is consistent with results from studies with other treatments for HAE [4, 5, 13, 14]. The faster relief and resolution of abdominal attacks compared with peripheral attacks is thought to be due to the lower degree of edema in submucosal tissue, or to faster resorption of edema fluid, as compared with subcutaneous tissue [4, 5, 13, 14]. A subgroup analysis of rhC1INH-treated attacks limited to those with upper airway involvement indicated a faster onset of relief [16] than for the entire oro-facial/ pharyngeal/ laryngeal reported in this study, which likely reflects the slower improvement of the facial (subcutaneous) edema of this broad category [17].

The results of the OLE presented here indicate that rhC1-INH provides fast-onset of relief with a high rate of therapeutic response, but without the potential risk of pathogenic transfer inherent to human blood-based products. In addition, the adverse event profile for rhC1-INH treatment reported here is similar to that reported other clinical studies with C1-INH, [5-7].

Conclusions

Whilst optimal efficacy can be achieved with the approved 50 U/kg dosing regimen, data from this OLE study indicate that a single-vial dose of rhC1-INH (2100 U) was effective in treating more than half of the HAE attacks. In addition, the effectiveness of treatment was maintained throughout subsequent attacks, irrespective of attack location. Treatment with rhC1-INH was well tolerated with a favorable safety profile.

Glossary

C1-INH: C1 inhibitor protein; HAE: hereditary angioedema; rhC1-INH recombinant human C1-INH; OLE: open-label extension phase; TEAE: treatment-emergent adverse event; VAS: visual analogue scale.

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Conflict of interest

DMOL has provided expert consultation services and received speaker honoraria and research funding from Pharming Technologies BV and Shire Human Genetic Therapies Inc. He has also received research funding from CSL Behring. **ARES** has received funding for research of angioedema from Pharming Technologies BV, Shire Human Genetic Therapies Inc., CSL Behring and Dyax Corp. He also is a member on the global advisory board of Shire Human Genetic Therapies Inc. **JFAB** has provided expert consultation services and received speaker honoraria and research funding from Pharming Technologies BV. **SKIV** has received research funding from Pharming, CSL Behring, Shire, Dyax. **ETOU**, **MSHL** and **GREA** have no conflict of interest to declare. **MTRI** has received research support from Pharming and honoraria and speaker's fees from CSL Behring and Shire Human Genetic Therapies Inc. **VMON** has received honoraria from Pharming Technologies BV, CSL Behring and Shire Human Genetic Therapies Inc. **ECIL** has received research support from Shire and honoraria and speaker's fees from CSL Behring. **MCAN** received speaker honoraria from CSL Behring and acted as a paid consultant to Shire Italia SpA. **SVIS** and **AREL** are employed by Pharming Technologies BV. **AZAN** is an advisor for Shire Human Genetic Therapies Inc. and has been an invited speaker for Shire Human Genetic Therapies Inc. and CSL Behring. **MCIC** has consultancy agreements with Dyax, Pharming Technologies BV and Shire Human Genetic Therapies Inc., is an advisor for Dyax, Shire Human Genetic Therapies Inc. and CSL Behring, and has been an invited speaker for Dyax, Shire Human Genetic Therapies Inc., CSL Behring, Pharming and ViroPharma.

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Legend to figures

Figure 1: Kaplan–Meier plot of the time to the onset of relief for Attacks 1–5

Figure 2: Kaplan–Meier plot of the time to the onset of minimal symptoms for Attacks 1–5

Figure 3: Response rates for Attack 1–5

Foot note to Figure 3: Response rate defined as relief in < 4 h.

Tables

Table 1: Overview of treated patients in the OLE by country

Participating Country	Number of centers per country	Number of treated patients in the OLE (N)	Number of treated attacks in the OLE (N)
<i>Argentina</i>	<i>1</i>	<i>5</i>	<i>19</i>
<i>Israel</i>	<i>5</i>	<i>21</i>	<i>61</i>
<i>Italy</i>	<i>8</i>	<i>17</i>	<i>30</i>
<i>Romania</i>	<i>1</i>	<i>14</i>	<i>84</i>
<i>Spain</i>	<i>4</i>	<i>0</i>	<i>0</i>
<i>The United Kingdom</i>	<i>2</i>	<i>0</i>	<i>0</i>
<i>total</i>	<i>21</i>	<i>57</i>	<i>194</i>

Table 2: Baseline characteristics for the overall open-label study population and subgroups of patients

	Total population (N = 57)
Age, mean $\pm$ SD (range)	36.3 $\pm$ 15.6 (16–68)
Male gender, n (%)	20 (35%)
BMI, mean kg/m ² (range)	25.6 (19–40)
Caucasian, n (%)	57 (100)
Alcohol use, mean units/wk	0.4
Smoking, # of cigarettes mean/wk	21.4

wk = week

Table 3: Baseline VAS and location of attack, by attack number

	Attack #1 (n = 50)^a	Attack #2 (n = 41)	Attack #3 (n = 30)	Attack #4 (n = 15)	Attack #5 (n = 10)	Total study population (N=57)
Baseline VAS						
(time -1h)	81.4 ±	79.0 ±	81.8 ±	83.3 ±	86.4 ±	
mean ± SD ^b	14.96	12.82	14.25	11.84	15.47	
Anatomical locations of edema ^c						
Abdominal, n (%)	25 (51%)	16 (39%)	15 (50%)	8 (53%)	7 (70%)	38 (67%)
OFPL, n (%)	15 (31%)	11 (27%)	12 (40%)	5 (33%)	2 (20%)	24 (42%)
Peripheral, n (%)	14 (29%)	16 (39%)	6 (20%)	3 (20%)	1 (10%)	29 (51%)
Genitourinary, n (%)	2 (4%)	2 (5%)	1 (3%)	1 (7%)	0	5 (9%)

^a 7 patients had their first attack in the randomized, controlled phase of the study and are therefore not listed under Attack 1

^b The baseline VAS scores of one patient was omitted from all VAS analyses due to a lack of overall VAS data during Attack 1

^c Some patients had multiple anatomical locations involved, e.g. abdominal + peripheral attacks, for each eligible attack

BMI = body mass index; OFPL= Oro-facial/ pharyngeal/ laryngeal; SD = standard deviation; VAS = visual analogue scale (0–100 mm; 0 = no symptoms, 100 = extremely disabling);

Table 4: Overview of mean body-weight and Body-Mass Index per treatment dose

	All treatments	Treatments with 2100 U	Treatments with 4200 U	Treatments with 6300 U*
Number of attacks (% of total)	194 (100%)	110 (57%)	68 (35%)	16 (8%)
Range BW (kg)	43.8 – 120.0	53.2 – 110.7	43.8 – 120.0	52.5 – 100.1
Mean BW (kg)	72.9	72.3	73.3	75.0
Range BMI (Kg/m ²)	18.5 – 40.6	18.8 – 33.3	18.5 – 40.6	21.0 – 32.7
Mean BMI (Kg/m ²)	26.4	26.0	27.1	26.2

*Includes one treatment with 10500 U of rhC1INH

Table 5: Primary and secondary outcomes (min) listed by location of attack, for the overall study population

Outcome	Abdominal (n = 80)	Peripheral (n = 21)	OFPL (n = 20)	Genitourinary (n = 1)
Overall study population				
Median time to initial symptomatic relief*	33	61	120	480
Median time to minimal symptoms**	240	265	723	1385

*Defined as a decrease in VAS of ≥ 20 mm;

**Defined as a VAS <20 mm

OFPL = Oro-facial/ Pharyngeal/ Laryngeal

Table 6: Common Adverse Events (AE) ($\geq 3\%$ of the study population) with onset dates within 7 days after receiving rhC1INH treatment, n (%).

	rhC1INH 2100 U single dose (n = 43)	rhC1IN 2100 U + additional dose (n=34)
total number of attacks treated	112 (57%)	82 (43%)
Number of patients experiencing at least one AE	12 (28%)	9 (26%)
Headache	1 (2%)	2 (6%)
Diarrhoea	1 (2%)	0
Nausea	1 (2%)	2 (6%)
Vertigo	0	1 (3%)

The safety set was analyzed for TEAEs and comprised 57 patients; 27 patients reported at least one TEAE; most events were mild-to-moderate in severity; total population = AEs occurring in all attacks, not just attacks 1–5; only those AEs occurring in >1 patient of the total population are listed. TEAE = treatment-emergent adverse events; Counts represent number of patients, not number of events

Table 7: Efficacy endpoints for patients with confirmed anti-C1INH antibodies

Patient	Anti-C1INH finding	Sample time point	Subsequent attack	Dose Administered	Time to beginning of relief (min)	Time to minimal symptoms (min)
906	IgG	Attack 1: Day 90	Attack 2 Attack 3	2100 U 2100 U	120 30	1440 1635
902	IgM	Attack 3: Day 0, Day 22				
	IgG	Attack 3: Day 0, Day 22 Day 90	Attack 3	4200 U	240	720
	IgA	Attack 3: Day 0				
3107	IgG	Pre-exposure, Attack 1: Day 0, Day 22	Attack 1	2100 U	60	240
7126	IgG	Attack 1: Day 22 Attack 2: Day 0	Attack 2	2100 U	240	480

Pre-exposure: before receiving any rhC1INH treatment

Day 0: day of the attack, before receiving rhC1INH treatment

Day 22: 22 days after receiving rhC1INH treatment

Day 90: 90 days after receiving rhC1INH treatment





