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;3:417-23)**

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).