

Health-related quality of life with hereditary angioedema following prophylaxis with subcutaneous C1-inhibitor with recombinant hyaluronidase

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ABSTRACT

Background: To estimate health-related quality-of-life changes in patients with hereditary angioedema due to C1-inhibitor (C1-INH) deficiency who received subcutaneous C1-INH with recombinant hyaluronidase (rHuPH20) for attack prophylaxis in a randomized, double-blind, dose-ranging, cross-over study.

Methods: Patients with type I/II hereditary angioedema received 1000 U of C1-INH with 24,000 U of rHuPH20 or 2000 U of C1-INH with 48,000 U of rHuPH20 every 3–4 days for 8 weeks and then crossed over for another 8-week period. The study was terminated early as a precaution related to non-neutralizing antibodies to rHuPH20. The Angioedema Quality of Life questionnaire (AE-QoL) was administered at weeks 1 and 5 of both periods, and at 1 week after the second treatment period. Changes in AE-QoL scores were calculated over both treatment periods and within each treatment period for patients with ≥ 4 weeks of treatment.

Results: Forty-one patients had evaluable AE-QoL data, and 22 patients completed treatment. At screening, 43% of the patients were receiving intravenous C1-INH. A significant average AE-QoL total score decline (improvement) of -8.1 (95% confidence interval, -13.7 to -2.5) was observed from baseline to the end of the study, and significant AE-QoL score declines were observed in the Functioning, Fear/Shame, and Nutrition domains. Patients on 2000 U reported higher mean AE-QoL score declines in Functioning and Nutrition domains relative to the 1000 U dose. Overall, 43.9% of all the patients, 45.5% of the study completers, and 46.7% of the nonprophylaxis users at baseline on high treatment doses achieved a reduction in the AE-QoL total score of six points.

Conclusion: Despite early termination and prestudy prophylactic intravenous C1-INH use by 43% of the patients, improved AE-QoL scores were observed after ≤ 16 weeks of subcutaneous C1-INH–rHuPH20 prophylaxis.

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Hereditary angioedema (HAE) due to C1 inhibitor (C1-INH) deficiency (*i.e.*, HAE type I or II), is a rare, autosomal-dominant condition caused by 1 of >300

mutations in the *SERPING1* gene that result in decreased or dysfunctional C1-INH protein. The condition is characterized by spontaneous, recurrent attacks of angioedema that affect the abdomen, extremities, urogenital region, face, oropharynx, and/or larynx. Dependent on the location, the angioedema can be disabling, painful, and/or life threatening.^{1–6} HAE presentation varies unpredictably throughout a patient's life, with the onset of symptoms often seen in early childhood.^{7,8} The frequency and severity of attacks may vary throughout life.^{2,9–11} The estimated prevalence of HAE is 1 in 50,000 people worldwide.^{3,12}

Beyond the actual symptoms of an attack, the unpredictable onset of HAE attacks is a major burden for patients and severely impacts their health-related quality of life (HRQoL).¹³ A 2010 study in the United States of 457 patients with HAE concluded that HAE had a considerable humanistic burden to patients across Physical and Mental Health 12-item Short Form (SF-12) Health Survey domains; negatively impacted educa-

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tion, career, and work productivity; and compounded the substantial economic burden.¹⁴ A recent study of 186 European patients with HAE found that patients experienced substantial impairment physically and emotionally both during and between attacks, despite standard of care.¹⁵ Although several treatments are available, patients with HAE still have a significant burden of disease,¹⁶ and, to date, there has been a shortage of comprehensive analyses of the impact and burden of disease that encompasses all aspects relevant to HAE patients. In a phase III, randomized, placebo-controlled, cross-over study of 22 patients who received intravenous (IV), plasma-derived C1-INH, the patients had significantly better 36-item Short Form Health Survey (SF-36) scores after 12 weeks of C1-INH prophylaxis treatment compared with 12 weeks without prophylaxis treatment.¹⁷

So far, studies that evaluated HRQoL in patients with HAE used generic instruments, such as the SF-12 and SF-36 Health Surveys. Because generic HRQoL instruments may not accurately measure the specific HRQoL impairment associated with angioedema and the impact of effective treatment, we developed and validated the first symptom-specific tool for use in studying HRQoL in patients with angioedema, the Angioedema Quality of Life questionnaire (AE-QoL).¹⁸ In addition, we recently confirmed the convergent validity of the AE-QoL for studying HRQoL in 278 patients with recurrent angioedema (chronic spontaneous urticaria or HAE) and described its sensitivity to detect change over time. Further, we identified a minimal clinically important difference (MCID) of six points for the AE-QoL total score.¹⁹ The identification of the MCID is of critical importance for the effective interpretation of any patient-reported outcome instrument because it represents the minimal change of an instrument's results (score) that is really meaningful to the patient. In our study, we sought to evaluate changes in HRQoL by using the AE-QoL in patients with HAE who received subcutaneous human plasma-derived C1-INH with recombinant human hyaluronidase (rHuPH20) for the prevention of angioedema attacks in a randomized, double-blind, dose-ranging, cross-over study. A tissue permeability modifier, rHuPH20 (Hylenex; Halozyme Therapeutics, Inc., San Diego, CA) can assist subcutaneous dispersion and potentially improves bioavailability of a coadministered therapeutic agent.²⁰

METHODS

Patients

The detailed methods of this randomized, controlled, dose-ranging, cross-over study (NCT01756157) were previously described.²¹ Briefly, patients with a confirmed diagnosis of HAE who were ages ≥ 12 years

were eligible for the study. Patients who were receiving prophylactic IV C1-INH before study entry must have had ≤ 1.0 moderate or severe attack per month (average) during the 3 consecutive months before randomization and must have had ≥ 2.0 moderate or severe attacks per month (average) during the 3 consecutive months before starting prophylaxis therapy. Patients who were not receiving prophylactic IV C1-INH before study entry must have had ≥ 2.0 moderate or severe angioedema attacks per month (average) during the 3 consecutive months before randomization.

Patients were excluded if they met any of the following conditions: (1) any C1-INH therapy or any blood products for treatment or prevention of an angioedema attack within 7 days before the first dose of the study drug in period 1; (2) prophylactic IV C1-INH that exceeded the approved dosing regimen of 1000 U every 3 or 4 days (maximum weekly dose of 2000 U); (3) angioedema attack signs or symptoms within 2 days before the first dose of the study drug in the period 1; (4) any androgen therapy (*e.g.*, danazol, oxandrolone, stanozolol, testosterone) within 7 days before the first dose of the study drug in period 1; (5) a history of hypercoagulability (abnormal blood clotting); or (6) a diagnosis of acquired angioedema or known C1-INH antibodies.

Study Design

Patients received the study drug during two 8-week treatment periods separated by a washout period of ≥ 7 days but < 30 days. Patients were randomly assigned to receive either 1000 U of C1-INH with 24,000 U of rHuPH20 (hereafter referred to as 1000 U of C1-INH) during the first period, followed by 2000 U of C1-INH with 48,000 U of rHuPH20 (hereafter referred to as 2000 U of C1-INH) during the second period, or 2000 U of C1-INH during the first period, followed by 1000 U of C1-INH during the second period. Each dose of C1-INH with rHuPH20 was administered as a single 20-mL subcutaneous injection in the abdomen given every 3 or 4 days. Patients who previously used IV C1-INH for prophylaxis discontinued IV use at baseline. The primary objectives of this study were to evaluate the efficacy of C1-INH with rHuPH20 to prevent angioedema attacks and to assess the safety and tolerability of the two dosing regimens. Quality-of-life assessment was a secondary study objective.

AE-QoL Instrument

The validated, angioedema-specific, AE-QoL instrument^{18,19,22} consists of 17 questions, each with a five-point response scale. The recall period is 4 weeks. The scores are summarized into a total score and four domain scores for (1) Functioning, (2) Fatigue/Mood, (3) Fear/Shame, and (4) Nutrition. The total and domain

scores can reach 0–100 points; higher values indicate a higher impairment level.

Statistical Analyses

The patients were asked to complete the AE-QoL questionnaire during five visits on weeks 1 and 5 of the first treatment period (P1) and on weeks 1, 5 of the second treatment period and 1 week after the second treatment period (P2). Patients who discontinued the study were asked to complete the questionnaire at the discontinuation visit. For P1, responses for week 1 were used as baseline and responses for week 1 of P2 were used as end-of-period values for P1. For P2, responses for week 1 were used as baseline and responses for 1 week after the second treatment period were used as end-of-period values. For P1 and P2, if end-of-period responses were missing, then the last available responses for that period were used, provided that ≥ 28 days passed since the baseline visit date for that period. The cumulative treatment effect over the entire study was measured from the P1 baseline until the last available response date for the study.

Means and 95% confidence intervals (CI) for changes in AE-QoL total scores and domain scores were calculated for each patient for the two 8-week treatment periods and for the entire study period. Adjusted differences between the treatments were tested by using separate analysis of covariance mixed models (with random intercepts for patients to account for within-subject correlation) for the AE-QoL total score and the domain scores. In each model, the last assessment score was the dependent variable, with the treatment group as a between-subjects factor and with a baseline score included as a covariate, along with age, sex, C1-INH prophylactic use at baseline, and treatment sequencing (1000 U of C1-INH–2000 U of C1-INH or 2000 U of C1-INH–1000 U of C1-INH). The rate of patients who experienced an MCID²³ in the AE-QoL total score was compared by treatment group. MCID was defined as a decline in impairment by at least six points on the AE-QoL total score scale.¹⁹ Pearson correlations between the change in AE-QoL total score and the percentage change monthly attack frequency (relative to an historic baseline) were reported by treatment group.

Subgroup analysis by using only patients who completed the study was performed, despite a small sample of completers, to assess potential bias in the main analysis because characteristics of the patients who withdrew from the study could have been different across treatment arms. In addition, the potential effect of C1-INH prophylactic use at baseline was evaluated because it was regarded as likely that the patients without IV C1-INH prophylactic use at baseline had a greater HRQoL improvement in the study compared with patients who had no previous C1-INH prophylaxis. Furthermore, inclusion criteria were different for C1-INH

prophylactic users (explained above in the Methods section). Therefore, the data were stratified by IV C1-INH prophylactic use status at baseline. The two-sided *t*-test for means and χ^2 tests for categorical variables were reported. Results were considered significant at $p < 0.05$, with no adjustment of significance level for multiple testing. All statistical analyses were conducted by using SAS (SAS version 9.3; SAS Institute, Cary, NC).

RESULTS

Patient Disposition and Demographics

Data from 41 of 47 randomized patients were used in this analysis, of whom, 22 completed both treatment periods (Fig. 1). Of the six patients who were not included in this analysis, five discontinued before the fourth week of P1 and one did not complete the questionnaire at P1 baseline and discontinued the study at the end of P1. Of the 41 patients with evaluable AE-QoL data, 15 did not provide evaluable AE-QoL change values for P2. The mean (standard deviation) age of patients ($n = 41$) in this study was 40.2 ± 14.4 years, 73.2% were women, and 78.1% were from U.S. sites. Forty-three percent of the patients were receiving prophylactic IV C1-INH at screening. The washout period between P1 and P2 was a mean (standard deviation) of 13.1 ± 6.3 days and a median of 11.0 days, with a range of 7–29 days. Dosing was discontinued in August 2013, after discussions with the U.S. Food and Drug Administration as a precaution related to observations from other clinical programs conducted by different sponsors and due to the emergence and unexpected incidence and titer of non-neutralizing anti-rHuPH20 antibodies in 45% of the patients.²¹ The presence of antibodies was not associated with impaired efficacy or any adverse clinical effects.

HRQoL Improves from Baseline to the Last Available Assessment

Mean AE-QoL total scores significantly improved by -8.1 (95% CI, -13.7 to -2.5 ; $p = 0.007$) from baseline to the last available assessment (Table 1). Of the AE-QoL domain scores, significant mean improvements were observed in the domains of Functioning by -12.8 (95% CI, -20.9 to -4.7 ; $p = 0.003$), Fear/Shame by -10.3 (95% CI, -17.1 to -3.5 ; $p = 0.005$), and Nutrition by -7.6 (95% CI, -13.3 to -2.0 ; $p = 0.012$). The change from baseline to the end of the study in the Fatigue/Mood domain was not statistically significant.

Comparison of Changes in the AE-QoL Total Score and the Domain Scores by Treatment

The mean AE-QoL total score improvement from baseline to the last available assessment (separately over P1 or P2) for the 2000-U C1-INH treatment was 6.6 compared with 3.4 for the 1000-U C1-INH treat-

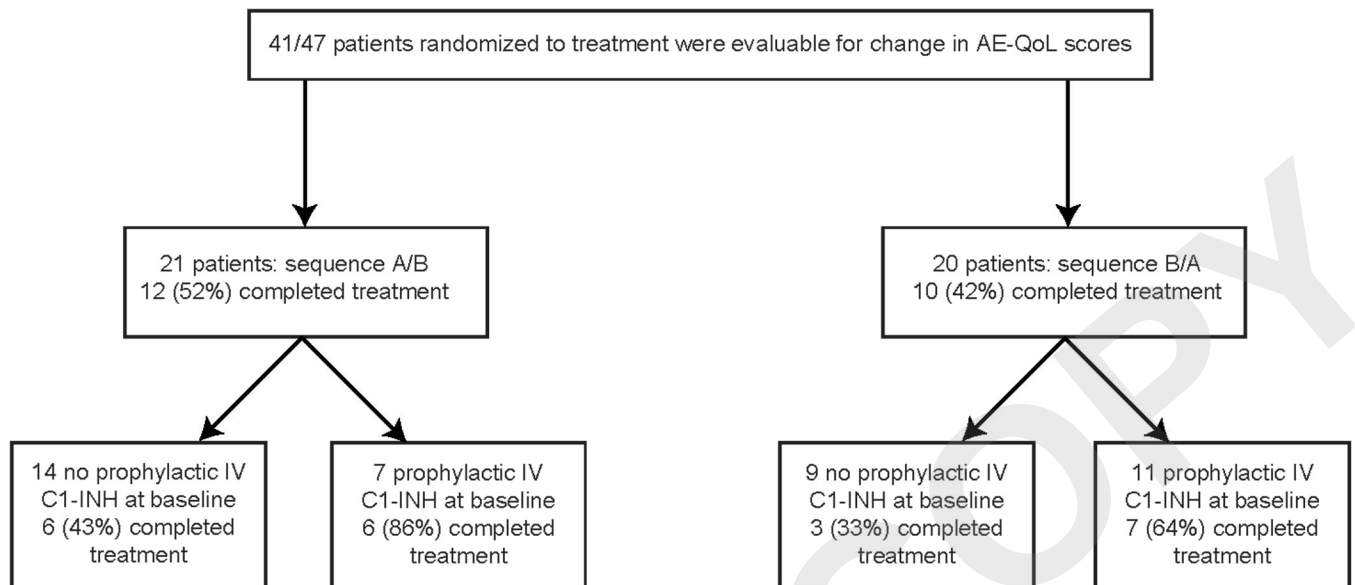


Figure 1. Disposition of patients by treatment sequence, baseline prophylaxis, and treatment completion. AE-QoL = Angioedema Quality of Life questionnaire; IV = intravenous; C1-INH = C1 inhibitor.

Table 1 Cumulative changes in AE-QoL scores for all the patients from baseline to last available assessment (N = 41)

AE-QoL Domain	Baseline Score, Mean $\pm$ SD	Last Available Assessment Score, Mean $\pm$ SD	Difference Between Baseline and the Last Available Assessment				
			Mean (95% CI)	$\pm$ SE	Median	Minimum, Maximum	<i>p</i> Value
Total score	36.26 $\pm$ 21.30	28.16 $\pm$ 21.16	−8.11 (−13.72 to −2.50)	18.34	−4.41	−44.12, 14.71	0.007
Functioning	32.62 $\pm$ 22.03	19.82 $\pm$ 22.36	−12.80 (−20.87 to −4.73)	26.37	−6.25	−62.50, 50.00	0.003
Fatigue/Mood	32.80 $\pm$ 24.08	30.85 $\pm$ 25.32	−1.95 (−8.66 to 4.76)	21.93	0	−50.00, 35.00	0.572
Fear/Shame	45.63 $\pm$ 26.56	35.37 $\pm$ 28.45	−10.26 (−17.06 to −3.46)	22.23	−8.33	−50.00, 37.5	0.005
Nutrition	24.09 $\pm$ 26.28	16.46 $\pm$ 21.37	−7.62 (−13.29 to −1.95)	18.51	0	−50.00, 25.00	0.012

AE-QoL = Angioedema Quality of Life questionnaire; SD = standard deviation; CI = confidence interval; SE = standard error.

ment (Table 2). After adjustments for baseline AE-QoL score, sex, age, baseline use of IV C1-INH prophylaxis, and study treatment sequence (not significant), the difference in mean AE-QoL score improvement between treatments was not statistically significant.

Subgroup Analysis of Mean Changes in AE-QoL Total Scores

Analysis of Study Completers. By focusing only on patients who fully completed both treatment periods, the mean (95% CI) AE-QoL total score was found to improve significantly from baseline to the last available assessment (over the whole study duration) by −10.23

(95% CI, −18.36 to −2.10; *p* = 0.0224) (Fig. 2). The mean difference between the treatment groups of −1.73 (95% CI, −12.37 to 8.90) was not statistically significant.

Influence of IV Prophylactic C1-INH at Baseline. When comparing patients who had used IV prophylactic C1-INH at baseline with those who had not, similar patterns were observed with better outcomes for the patients who had not used IV C1-INH prophylactically at baseline (Fig. 3). Mean (standard deviation) AE-QoL total scores at study baseline (week 1 of P1) were 34.23 $\pm$ 21.28 for the prophylactic users and 37.85 $\pm$ 21.23 for the nonusers, a nonstatistically significant difference. In previous prophylaxis users, the mean

Table 2 Comparison of mean change in AE-QoL scores by treatment

AE-QoL Domain	Unadjusted Change From Period Baseline to Last Available Period Assessment, Mean $\pm$ SD		Adjusted Results*		
	1000 U of C1-INH (n = 34)	2000 U of C1-INH (n = 33)	Treatment Effect#	95% CI	p Value
Total score	-3.42 $\pm$ 16.27	-6.64 $\pm$ 17.97	-0.96	-9.16 to 7.25	0.8118
Functioning	-4.23 $\pm$ 22.86	-12.50 $\pm$ 28.43	-6.45	-17.66 to 4.76	0.2466
Fatigue/Mood	-0.74 $\pm$ 23.42	-0.76 $\pm$ 21.69	1.69	-8.92 to 12.29	0.7453
Fear/Shame	-5.88 $\pm$ 17.23	-6.94 $\pm$ 20.40	1.98	-7.29 to 11.25	0.6631
Nutrition	-1.10 $\pm$ 16.68	-8.71 $\pm$ 19.13	-5.34	-13.64 to 2.96	0.1965

AE-QoL = Angioedema Quality of Life questionnaire; SD = standard deviation; C1-INH = C1 inhibitor; CI = confidence interval; ANCOVA = analysis of covariance; P2 = second treatment period; P1 = first treatment period.

*Adjusted treatment effect from repeated measurements ANCOVA mixed model for AE-QoL score at P2 with covariates: baseline AE-QoL score at P1, sex, age, baseline C1-INH prophylactic use, and study treatment sequence.

#A negative difference indicates the advantage for the 2000-U C1-INH treatment.

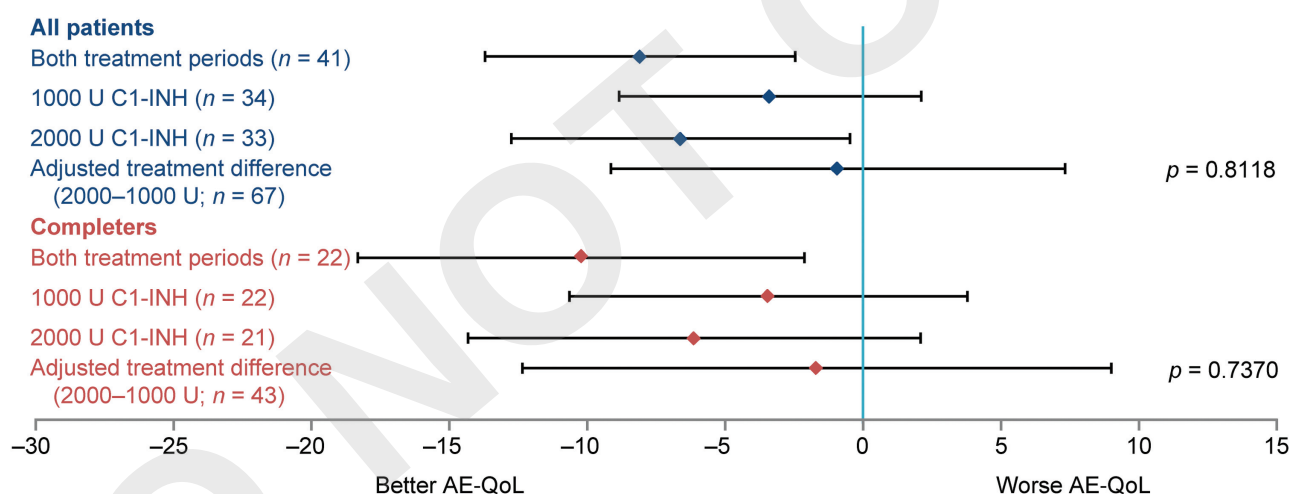


Figure 2. Mean changes from baseline in AE-QoL total scores; all the patients and the patients who completed both treatment periods (completers). Bars represent 95% CIs. “Both treatment periods” include the cumulative treatment effect for all patients when using week 1 of P1 as the baseline until the last available response date for the study (last observation carried forward). AE-QoL = Angioedema Quality of Life questionnaire; CI = confidence interval; C1-INH = C1 inhibitor; P1 = first treatment period.

(95% CI) AE-QoL total score improvement from baseline to last available assessment (over the whole study duration) was -6.05 (95% CI, -13.96 to 1.86), a non-statistically significant difference compared with -9.72 (95% CI, -17.67 to -1.77) in those who were not using prophylaxis at baseline. AE-QoL total score improvements in previous prophylaxis users were -1.30 for the 1000-U C1-INH treatment and -4.82 for the 2000-U C1-INH treatment compared with -5.54 and -8.82, respectively, for those who were not using prophylaxis at baseline. Differences between treatments for patients who used prophylaxis at baseline and separately for those who did not use prophylaxis at baseline were not statistically significant. The adjusted differences between treatments for each sub-

group of baseline prophylaxis use were not statistically significant.

MCID in AE-QoL Total Scores

Over the study duration, 43.9% of all the patients and 45.5% of the patients who completed the study had an improvement from baseline in the AE-QoL total score of six or more points, which is the MCID (Fig. 4). Among all the patients, 45.5% achieved the MCID with the 2000-U C1-INH treatment compared with 26.5% for the 1000-U C1-INH treatment, but the difference between the treatments was not statistically significant. Among the patients who completed both treatment periods, 38.1% achieved the MCID with the high dose compared with 27.3% with the low dose. Over the study duration,

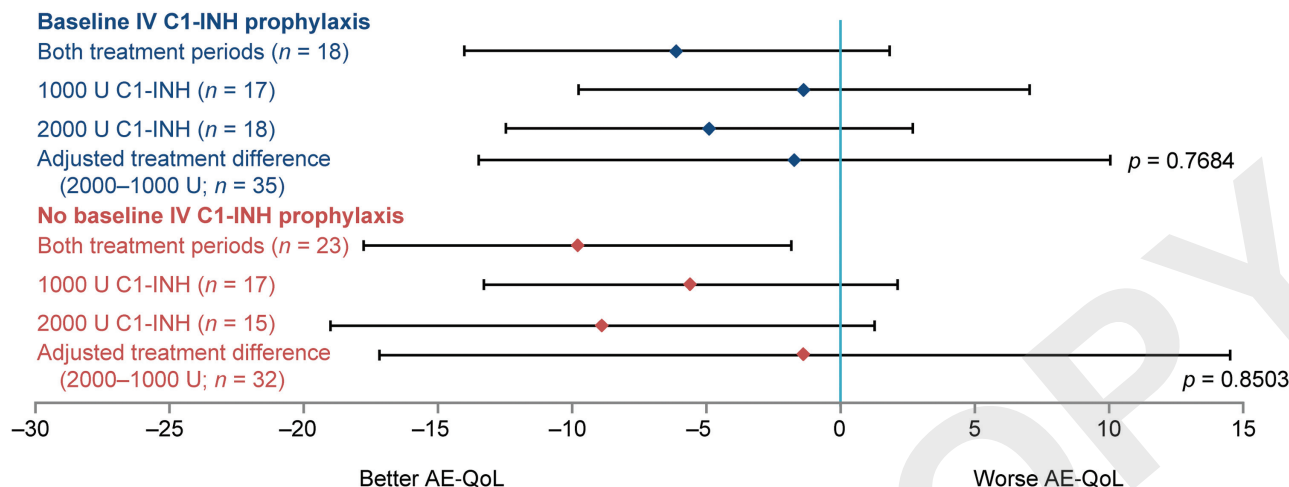


Figure 3. Mean changes in AE-QoL total scores by baseline IV C1-INH prophylaxis status. Bars represent 95% CIs. “Both treatment periods” include the cumulative treatment effect for all the patients when using week 1 of P1 as the baseline until the last available response date for the study (last observation carried forward). AE-QoL = Angioedema Quality of Life questionnaire; IV = intravenous; C1-INH = C1 inhibitor; CI = confidence interval; P1 = first treatment period.

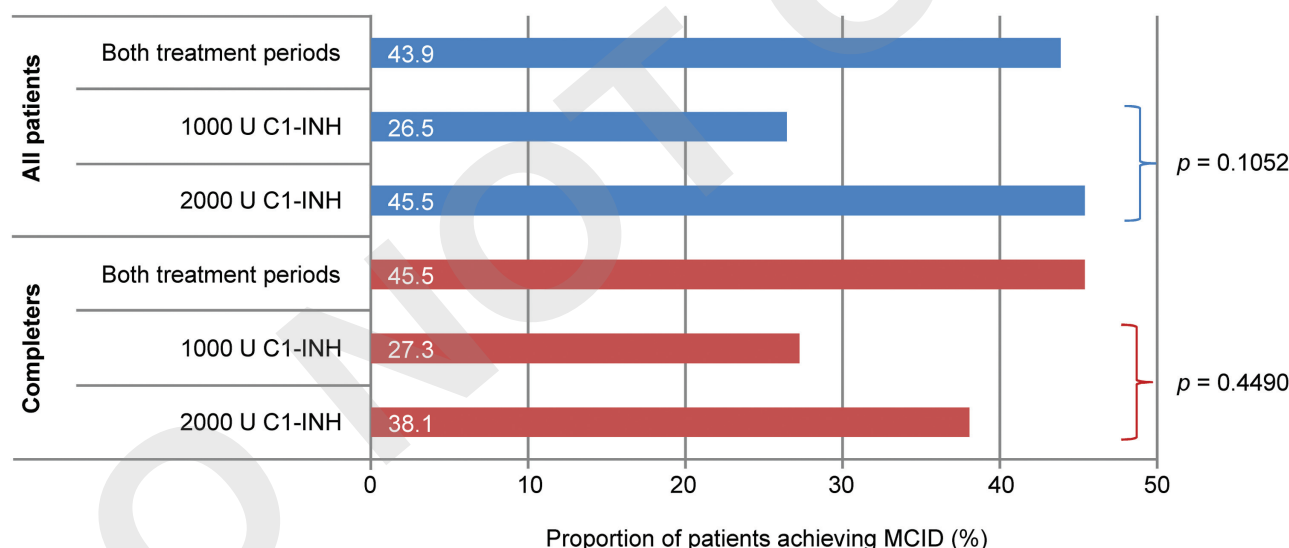


Figure 4. Proportion of patients who achieved the MCID of the AE-QoL total score. “Both treatment periods” include the cumulative treatment effect for all the patients by using week 1 of P1 as the baseline until the last available response date for the study (last observation carried forward). “Completers” was defined as the patients who completed both treatment periods. MCID = Minimal clinically important difference; P1 = first treatment period; C1-INH = C1 inhibitor.

44.4% of patients who used IV C1-INH prophylaxis at baseline achieved the MCID in total AE-QoL compared with 43.5% of the patients who did not have IV C1-INH prophylaxis at baseline (Fig. 5). Within the subgroups of baseline IV C1-INH prophylaxis use, the differences between the treatments in the percentage of patients who achieved the MCID in AE-QoL total score numerically favored the 2000-U C1-INH treatment but was not statistically significant.

Correlation of Changes in AE-QoL Total Score and Frequency of Attacks

For the patients on both low and high doses, positive correlations of 0.28 and 0.25 were found between the

change in total AE-QoL and the percentage change in monthly frequency of attacks from baseline.

DISCUSSION

Previous studies show that patients with HAE have a significant burden of illness similar to that of severe asthma or Crohn’s disease.¹⁴ Angioedema attacks are unpredictable, painful, and debilitating, and impair a patient’s ability to function. Disfiguring attacks and anticipation of future attacks can result in anxiety, depression, and impaired social function.^{14,24} In a randomized, placebo-controlled, cross-over study, prophylactic use of IV C1-INH concentrate reduced

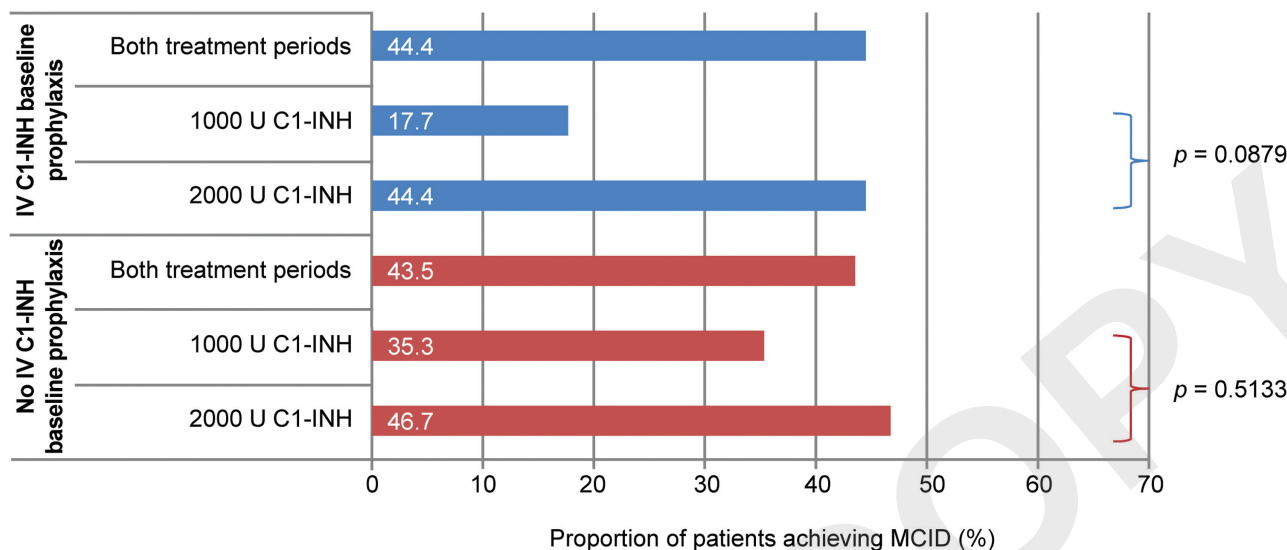


Figure 5. Proportion of patients who achieved the MCID of the AE-QoL total score by baseline IV C1-INH prophylaxis status. “Both treatment periods” include the cumulative treatment effect for all the patients when using week 1 of P1 as the baseline until the last available response date for the study (last observation carried forward). MCID = Minimal clinically important difference; IV = intravenous; C1-INH = C1 inhibitor.

the frequency, severity, and duration of attacks in patients with HAE.²⁵ The patients also showed improvement in HRQoL as measured by SF-36.¹⁷ The magnitude of improvement was similar to or greater than that observed after effective treatment of other chronic diseases characterized by intermittent attacks and/or episodes, including epilepsy,^{26,27} asthma,^{27,28} and migraine.²⁹

In the present study, we evaluated the effect of subcutaneous C1-INH prophylaxis in patients with HAE by using the AE-QoL questionnaire, which was specifically developed to measure the burden of angioedema. Analysis of the results indicated that patients had significant improvement in angioedema-related quality-of-life impairment during treatment with subcutaneous C1-INH compared with baseline. These improvements were positively correlated with a reduction in the frequency of HAE attacks. As expected, improvements in AE-QoL total scores were better for patients who fully completed the study and those who had not used IV C1-INH prophylaxis at baseline before starting subcutaneous C1-INH prophylaxis during the study. The patients who completed the study had a mean improvement from baseline in AE-QoL total score (-10.2) that was statistically significant and exceeded the MCID for the AE-QoL. Approximately 44% of all the patients, 45% of those who completed the study, and 43% of those who had not used IV C1-INH prophylactically at baseline achieved the MCID. Functioning, Fear/Shame, and Nutrition were the domains with the greatest improvement from baseline.

Although the results did not show a statistically significant difference between the treatment groups, the

improvements from baseline in AE-QoL scores were numerically higher for the higher dose (2000 U of C1-INH) compared with the lower dose (1000 U of C1-INH). This result reflected the clinical outcomes of the study in which the difference between the treatments in the reduction from baseline in the number of angioedema attacks per month was numerically higher for the higher dose treatment but the difference was not statistically significant.²¹ Because the study was terminated early and only 22 patients completed both treatment periods, the study may have been underpowered to detect a difference between the doses. A sample size of 40 patients was planned for the study, with an expectation that 34 patients would complete both treatment periods.

Patients who had not previously received prophylactic IV C1-INH at baseline had greater improvements in AE-QoL total score compared with those who had received IV C1-INH at baseline. This result may be related to the study entry criteria, which required patients who were receiving IV C1-INH at baseline to have a history of ≤ 1.0 moderate or severe attacks per month during the 3 consecutive months before randomization. Patients who were not receiving IV C1-INH at baseline must have had ≥ 2.0 attacks per month during that period. Thus, the baseline AE-QoL scores for these two subgroups were measured under different levels of angioedema attack frequency, and the mean AE-QoL scores at study baseline indicated slightly lower impairment in patients who received prophylactic IV C1-INH. Furthermore, the patients who were already receiving prophylactic C1-INH before the study may have had more severe disease than

those who were not receiving prophylactic C1-INH therapy because patients who are candidates for prophylactic C1-INH therapy typically have a high disease burden.¹³

This study had several limitations. HAE is a rare disease, and the number of patients in this analysis was comparatively small ($n = 41$). Approximately half of these patients did not complete the study because it was terminated early, and the study was underpowered to detect a difference between the dose groups in the primary end point (the number of attacks per month). Furthermore, the different entry criteria based on IV C1-INH use at baseline may have introduced more variability in baseline HRQoL than a study population that consisted solely of patients with ≥ 2.0 attacks per month. These factors may have limited the power of this analysis to detect a significant difference between the dose groups in HRQoL. Another potential limitation of the study design was the use of the P2 baseline AE-QoL measurement as the end-of-period measurement for P1. This could have led to an underestimation of both treatment effects during P1, which made these results conservative. However, given the relatively short average washout period of slightly < 2 weeks, a nonsignificant study sequence effect, and both study arms that consisted of active treatment, it was not likely that this measurement design caused substantial bias. Also, this limitation did not apply to the findings related to the AE-QoL changes over the entire study (P1 baseline to the end of the second treatment period).

CONCLUSION

Despite these limitations, the results of this study showed that patients who received subcutaneous C1-INH with the dispersing agent rHuPH20 every 3 to 4 days for 2 months had clinically and statistically significant improvement from baseline in HRQoL as measured by the AE-QoL. To our knowledge, this was the first study that demonstrated an improvement in HRQoL with subcutaneous C1-INH. In addition, $\sim 44\%$ of patients previously on IV C1-INH prophylaxis met the MCID after transition to the subcutaneous C1-INH formulation. Future studies of HAE therapies should evaluate HRQoL outcomes as well as clinical outcomes to more fully characterize the benefit-risk profiles of these therapies.

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