

Quality of life in patients with hereditary angioedema receiving therapy for routine prevention of attacks

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ABSTRACT

Patients with hereditary angioedema (HAE) have impaired health-related quality of life (HRQoL), but the effect of preventative treatment strategies on HRQoL has not been evaluated. This study was designed to evaluate the effect of routine prevention therapy with nanofiltered C1 inhibitor (C1 INH-nf; human) on the HRQoL of patients with HAE. Thirty-six-item Short Form (SF-36) Version 1.0 questionnaires were administered at the beginning and end of two 12-week treatment periods in this multicenter, randomized, placebo-controlled, crossover study. Patients ($n = 22$) received intravenous injections of 1000 U of C1 INH-nf or placebo every 3–4 days for 12 weeks and then crossed over to the other treatment arm for a second 12-week period. Patients could receive open-label C1 INH-nf (1000 U) for the acute treatment of angioedema attacks in either arm of the study. Sixteen patients had evaluable SF-36 data. Mean physical component summary scores (PCSSs) were 36.41 at baseline, 37.06 at the end of the placebo period, and 43.92 at the end of the C1 INH-nf period. Mean mental component summary scores (MCSSs) were 49.90, 44.98, and 54.00, respectively. Least square mean differences (95% confidence intervals) between C1 INH-nf and placebo in norm-based SF-36 scores at the end of each treatment period were 6.55 (1.48, 11.62; $p = 0.015$) for PCS and 8.70 (1.67, 15.72; $p = 0.019$) for MCS. In a clinical trial setting, patients with HAE had significantly better HRQoL after 12 weeks of C1 INH-nf for routine prevention compared with acute treatment of individual angioedema attacks in the absence of routine prevention while on placebo. This study was a part of the clinical trial NCT01005888 registered in www.clinicaltrials.gov.

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Hereditary angioedema (HAE) due to C1 inhibitor (C1 INH) deficiency is a rare, autosomal dominant disorder characterized by recurrent, unpredictable episodes of angioedema which causes swelling in the extremities, intestines, external genitalia, face, or oropharynx.¹ Abdominal attacks may be associated with significant pain, nausea, and vomiting and may lead to hospitalization and unnecessary exploratory surgery. Laryngeal attacks are associated with a substantial risk of death from asphyxiation, particularly in patients who are undiagnosed.² Subcutaneous swelling of the face, hands, and feet can be debilitating and impede activities of daily living.^{3,4}

The pain and disability caused by HAE has a negative impact on patients' health-related quality of life (HRQoL).^{3–7} Patients with HAE have been shown to have lower mental component scores (MCSSs) and physical component summary scores (PCSSs) of the 36-item Short Form (SF-36) than the general population.^{6,8} Pain, swelling, and disability affect physical and mental health at the time of an attack.⁷ Between attacks, patients may have anxiety about future attacks.⁹ These effects may lead to depression, the symptoms of which have been shown to be common in patients with HAE.^{6,10}

Treatment approaches for patients with HAE include acute treatment to reduce the severity and duration of individual attacks and routine prophylaxis to prevent attacks from occurring. Although previous studies allowed us to evaluate the HRQoL of patient with HAE have impaired HRQoL, the effect of preventative treatment strategies on HRQoL has not been evaluated. In this study, we evaluated the HRQoL of patients who received C1 esterase inhibitor (human; CINRYZE [ViroPharma, Inc., Exton, PA]; nanofiltered C1 INH [C1 INH-nf]) for the routine prevention of angioedema attacks in the context of a randomized, placebo-controlled, crossover study. During the study, in addition to regular infusions of study medication (C1 INH-nf or placebo) every 3 or 4 days, patients could receive open-label C1 INH-nf for the acute treatment of angioedema

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attacks at any time. Therefore, the crossover study design allowed us to evaluate the QoL of patients while they were receiving two different treatment approaches: routine prevention (C1 INH-nf infusions every 3 or 4 days with the option of acute treatment in the event of a breakthrough attack) and acute treatment in the absence of routine prevention (placebo infusions every 3 or 4 days with the option of acute treatment in the event of an attack).

METHODS

This study was approved by the institutional review boards at all sites. The methods of this multicenter, randomized, placebo-controlled, crossover study were previously described in detail.¹¹ Briefly, patients ≥ 6 years old with a confirmed diagnosis of HAE and a history of two or more attacks per month were eligible. Patients received intravenous injections of 1000 U of C1 INH-nf or placebo every 3 to 4 days for 12 weeks and then crossed over to the other treatment arm for a second 12-week period. Patients could receive open-label C1 INH-nf (1000 U) for the acute treatment of angioedema attacks in either arm of the study. All infusions were administered at the study site. All patients provided informed consent and the protocol was approved by each study site's Institutional Review Board. Patients recorded the location, severity, and duration of angioedema attacks in diary cards. Attack severity was graded as mild (1), moderate (2), or severe (3).

SF-36 Version 1.0 questionnaires^{12,13} were administered at the beginning and end of each of the two 12-week treatment periods. The questionnaire completed at the beginning of the first treatment period was considered to be the baseline questionnaire. Because most questions in the SF-36 ask for the patient to report how they felt during the last 4 weeks and the median washout period between the first and second treatment periods was 5.5 days (range, 2–13), the questionnaire completed at the beginning of the second treatment period was considered to be duplicative of that of the end of the first treatment period. If the patient did not complete the questionnaire at the end of the first treatment period, the questionnaire completed at the beginning of the second treatment period was used for the end of the first treatment period. Only patients who completed SF-36 questionnaires at baseline, in between treatment periods, and at the end of the second treatment period were included in the analysis. The SF-36 questionnaire is only valid for adults, so patients <18 years old did not complete SF-36 questionnaires.

Assessment of HRQoL using SF-36 scores was a pre-specified secondary end point of this study. Responses to SF-36 questionnaires were used to calculate PCSs

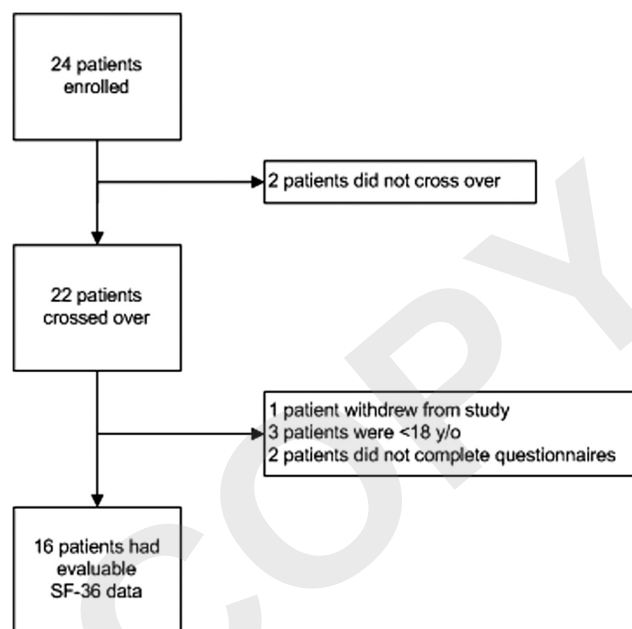


Figure 1. Patient disposition.

and MCSs and the eight individual domain scores: physical function, role physical, bodily pain, social function, mental health, role emotional, vitality, and general health.^{12,13} Higher scores are indicative of better HRQoL. Norm-based SF-36 scores were computed for comparison with the score for the general population of the United States (mean, 50; SD, 10).

A mixed-model ANOVA with a period effect, a treatment effect, and adjustment for the baseline score was used to evaluate the differences in SF-36 scores while patients received C1 INH-nf or placebo. Models were initially fit with a carryover effect (*i.e.*, a treatment-by-period interaction or sequence effect); however, the carryover effect was to be removed from the final model if it was not statistically significant. A repeated-measures approach, accounting for within-patient correlation, was used. Each patient only contributed two follow-up observations, so no assumptions about the within-patient correlation structure were required, beyond assuming that the correlation was nonzero. The models were fit with SAS Version 9.2 PROC MIXED (SAS/STAT Version 9.22; SAS Institute, Inc., Cary NC).

RESULTS

Twenty-four patients were enrolled in the study (Fig. 1). Two of these did not participate in the second treatment period, did not contribute corresponding attack rate and efficacy data, and were excluded from all analyses. Sixteen of the 22 randomized patients who crossed over completed SF-36 questionnaires at baseline, in between treatment periods, and at the end of the second treatment period. One of the 16 patients did not complete the questionnaire at the end of the first

Table 1 Demographic characteristics and attack rates for patients included in the analysis and those excluded from the analysis

	Patients Included in Analysis <i>n</i> = 16	Patients Excluded from Analysis <i>n</i> = 8
Randomized to receive placebo first, <i>n</i> (%)	7 (43.8)	5 (62.5)
Female, <i>n</i> (%)	14 (87.5)	7 (87.5)
Age (yr), mean $\pm$ SD	41.69 $\pm$ 14.95	32.13 $\pm$ 18.96
Attacks/month on placebo,* mean $\pm$ SD	4.20 $\pm$ 1.40	4.20 $\pm$ 1.68
Attacks/month on C1 INH-nf,* mean $\pm$ SD	2.24 $\pm$ 1.96	2.24 $\pm$ 1.40

**Attack rate is defined as the total number of attacks associated with the period divided by the duration (months) for that period. C1 INH-nf = nanofiltered C1 inhibitor.*

treatment period, so the answers from the questionnaire completed 6 days later at the beginning of the second treatment period were used in the analysis. The 6 of 22 patients who were excluded from the analyses included 1 patient who withdrew from the study during the second treatment period and did not complete the final questionnaire, 3 patients who were <18 years old and could not complete SF-36 questionnaires because of age limitations, and 2 patients who were from a study site that did not administer SF-36 questionnaires (Fig. 1). The majority (87.5%) of patients included in the analysis were women. The mean ($\pm$ SD) age was 41.69 $\pm$ 14.95 years. As previously reported,¹¹ patients (*n* = 22) had a twofold reduction in the mean number of attacks during the 12-week treatment period while receiving C1 INH-nf (6.26 attacks) compared with placebo (12.73 attacks; *p* < 0.001); the sequence effect (*p* = 0.54) and period effect (*p* = 0.42) were not statistically significant. For the purposes of this analysis, attack rate data were converted to mean number of attacks per month (Table 1). Because the three patients who were <18 years old could not complete the SF-36 questionnaire, the overall mean age of patients excluded from the analysis was slightly younger than that of patients who were included (Table 1). However, the attack rates were similar between the groups.

At baseline, the mean PCSs and MCSs were 36.41 $\pm$ 10.23 and 49.90 $\pm$ 9.96, respectively. The baseline mean PCS was well below the mean score of 50 for the general U.S. population. The individual domains that were most impaired at baseline were bodily pain, role physical, and social function, all of which were <40 or 1 SD below the general U.S. population.

SF-36 scores at the end of each 12-week period are presented according to treatment received (placebo or C1 INH-nf), irrespective of the treatment randomization sequence (Fig. 2). Mean SF-36 scores at the end of the placebo period were generally lower than or equal to baseline, whereas scores at the end of the C1 INH-nf period were generally greater than both placebo and

baseline. The PCS was 43.92 $\pm$ 12.84 after patients received C1 INH-nf for 12 weeks and 37.06 $\pm$ 11.60 after they received placebo; the MCS was 54.00 $\pm$ 7.82 and 44.98 $\pm$ 16.07, respectively. SDs of mean scores while patients received placebo (ranging from 10.41 to 16.19) were generally greater than those observed while patients received C1 INH-nf (ranging from 7.63 to 14.69; Fig. 2), indicating greater variability in SF-36 scores while patients were receiving placebo. In addition, despite the small sample size, the variability observed while patients received C1 INH-nf was consistent with that of the general U.S. population.¹⁰

Mean changes from baseline to the end of the C1 INH-nf period were generally positive, indicating improvement, while mean changes from baseline to the end of the placebo period were near zero, indicating no change, or were negative, indicating worsening (Fig. 3). The domains with the greatest impairment at baseline (bodily pain, role physical, and social function) were the domains in which the greatest improvement from baseline was observed with C1 INH-nf.

Statistical analysis of the least square mean differences between C1 INH-nf and placebo in norm-based SF-36 scores at the end of each treatment was conducted. The carryover effect, also known as the sequence effect or treatment-by-period interaction, was not statistically significant for any of the individual outcomes and was removed from all models. The results of the model revealed statistically significant differences between C1 INH-nf and placebo in both the PCSs and MCSs and each individual domain (Fig. 4).

DISCUSSION

The HRQoL of patients at the beginning of this study was indicative of the physical and emotional toll of experiencing frequent and unpredictable angioedema attacks. Baseline SF-36 scores showed that patients had significant physical impairment and some mental impairment, particularly in social function and general health. PCSs were lower than MCSs, while MCSs were

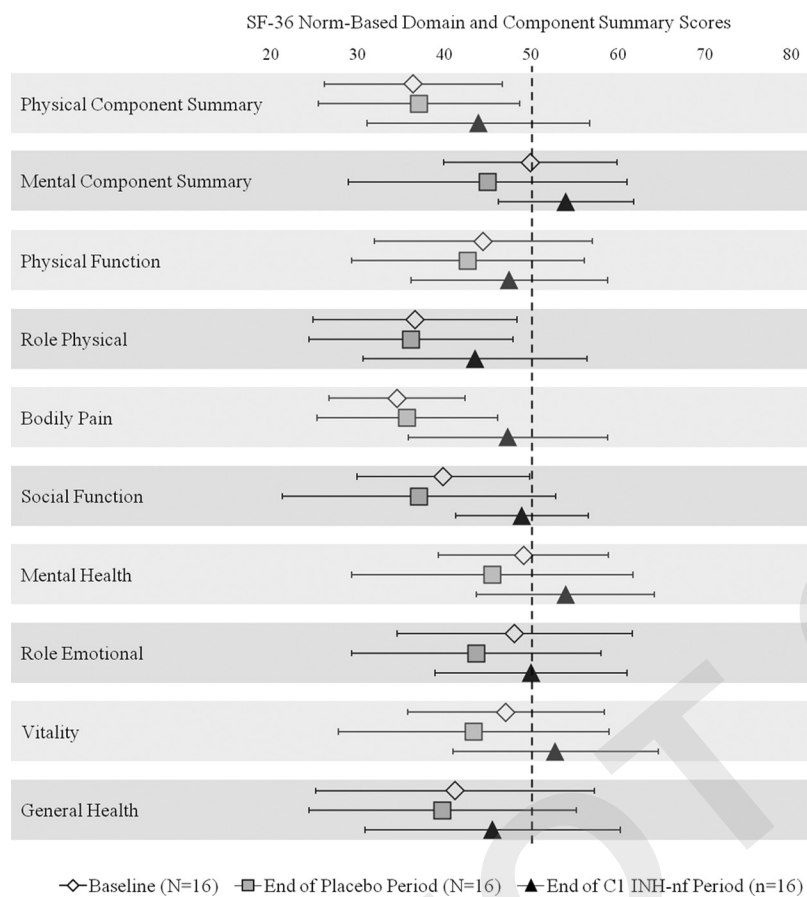


Figure 2. Mean (SD) norm-based 36-item Short Form (SF-36) domain scores and component summary scores at baseline, the end of the placebo period, and the end of the nanofiltered C1 inhibitor (C1 INH-nf) period. End of placebo or C1 INH-nf values were from both first and second 12-week treatment periods, depending on which randomization sequence patients underwent (i.e., placebo and then C1 INH-nf or C1 INH-nf and then placebo). For comparison, the mean score for the general U.S. population is 50 (dotted line) with an SD of 10.

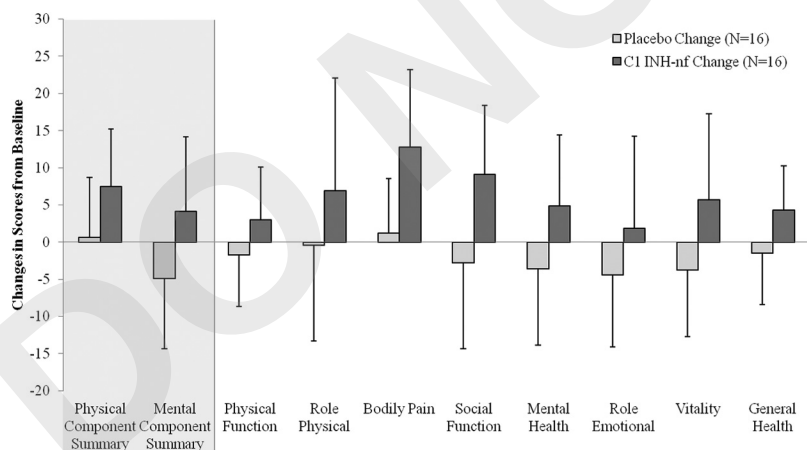


Figure 3. Mean (SD) changes in norm-based 36-item Short Form (SF-36) domain scores and summary scores from baseline to end of the placebo or nanofiltered C1 inhibitor (C1 INH-nf) period.

similar to the general population. In a previous study of French patients with HAE,⁵ the converse trend was observed; patients had more impairment in the MCS than the PCS. Our study population consisted of patients with more frequent attacks (median historical attack rate, 4.3 attacks per month; range, 2–9; data on file; ViroPharma, Inc., part of the Shire Group of Companies) than those of the French study, which may explain the differences between the studies. The lack of impairment in the MCS observed in our study may reflect the resilience of patients who have been coping

with their disease for many years and have accepted the disease burden as a regular part of life. This study was conducted before any of the newer therapies for HAE were available.

The randomized, placebo-controlled, crossover design of this study enabled us to evaluate the effect of routine prevention therapy on HRQoL. Current treatment guidelines recommend that all patients with HAE should have access to acute treatment for angioedema attacks, even those receiving routine prevention therapy.¹⁴ Although this study was designed before

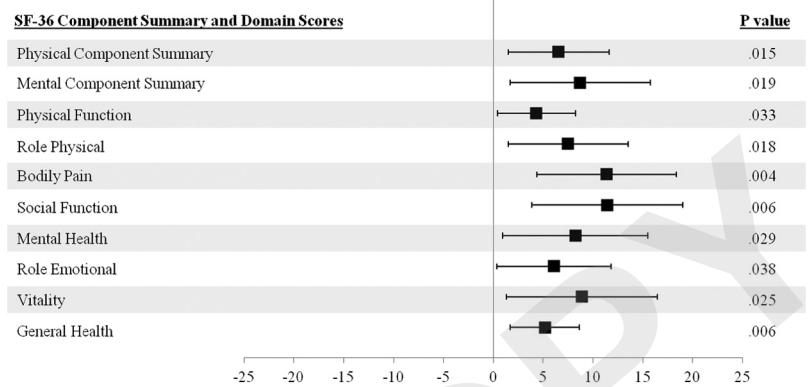


Figure 4. Least-square mean differences (nanofiltered C1 inhibitor [C1 INH-nf] minus placebo) and 95% confidence interval in norm-based 36-item Short Form (SF-36) scores at the end of each treatment period.

these guidelines were published, the study treatment regimens were consistent with this recommendation. Patients received double-blind C1 INH-nf or placebo for routine prevention and could receive open-label C1 INH-nf for the acute treatment of attacks at any time. Thus, patients received active study medication “on-demand” even during the “placebo” period of the study. Indeed, patients received a median of 13.5 (range, 2–34) open-label injections of C1 INH-nf during the placebo period (data on file; ViroPharma, Inc., part of the Shire Group of Companies). Therefore, the results of this study may underestimate the true effect of routine prevention with C1 INH-nf on HRQoL because patients were blinded to study medication treatment assignment for routine prevention but received open-label C1 INH-nf during the placebo period. Similarly, because of the placebo effect, the results may overestimate the true effect of acute treatment in the absence of routine prevention; patients were receiving blinded placebo injections in addition to acute therapy.

Despite these aspects of the study design, patients had significantly better QoL outcomes while receiving C1 INH-nf for routine prevention than while receiving placebo. The greatest magnitude of improvements from baseline and differences between C1 INH-nf and placebo were in the social function and bodily pain domains, which is consistent with our understanding of the burden of frequent angioedema attacks on HRQoL.^{3,6,9,15} However, significant differences between C1 INH-nf and placebo were observed for all individual domains. Efficacy results from this study showed that patients had a significant reduction in the frequency, severity, and duration of angioedema attacks while receiving C1 INH-nf compared with placebo.¹¹

The differences between treatment groups in the HRQoL measured by SF-36 scores observed in our study were similar to or greater than those observed in other chronic paroxysmal diseases that are characterized by intermittent attacks or episodes (*i.e.*, asthma, epilepsy, and migraines)^{16–19} that cause significant negative impacts on HRQoL. For example, the differ-

ence in PCSs observed between C1 INH-nf and placebo was approximately similar to the difference between patients with asthma that was at least well controlled versus not well controlled¹⁶ and approximately twice the difference in scores of patients with epilepsy after a 50% or greater reduction in seizure frequency compared with baseline.¹⁷ The improvement in MCSs between C1 INH-nf and placebo was ~1.5 times the difference observed in the asthma study¹⁶ and was similar to the difference observed in the epilepsy study.¹⁷ In comparison with these studies of asthma and epilepsy, the magnitude of the benefit of routine prevention treatment with C1 INH-nf in patients with HAE was clinically meaningful.

Previous studies have evaluated the impact of on-demand therapy on HRQoL outcomes in patients with HAE. In one study,²⁰ patients who received a different plasma-derived C1 INH product for acute treatment of individual attacks had favorable HRQoL outcomes. Although this study prospectively evaluated patients over time, treatment was administered in an open-label fashion, and there was no comparator group. In addition to these differences in study design, the results are difficult to compare with our study because most patients in the previous study had less disease burden (*i.e.*, less frequent attacks) than those in our study. In another study of the acute treatment of individual attacks,²¹ HRQoL improved when patients could self-administer plasma-derived C1 INH. However, self-administration was not available to the patients in our routine prevention study.

Several limitations must be considered when interpreting the results of this study. The SF-36 questionnaire is a general medical assessment tool used for many different diseases and may not adequately characterize the specific burdens associated with HAE. An angioedema-specific tool to assess HRQoL, such as those recently developed,^{22,23} was not available at the time this study was conducted. Generic instruments, such as SF-36, have been shown to be less sensitive than disease-specific HRQoL assessment instruments in other disease states.²⁴ In addition, most questions in

the SF-36 are based on a recall of how patients felt “within the past 4 weeks,” and patients’ responses may be highly dependent on whether they experienced an attack during that 4-week period. HAE is a rare disease, and the study population was small. However, the variability in SF-36 scores in patients receiving C1 INH-nf was consistent with that of the general U.S. population. Finally, the SF-36 Version 1 questionnaire was used, which captures a smaller range of potential levels of functioning in the role function scales compared with the SF-36 Version 2.0 and thus may be less sensitive to changes in these scales.

CONCLUSIONS

In a clinical trial setting, patients with HAE had significantly better HRQoL after 12 weeks of treatment with C1 INH-nf for routine prevention compared with acute treatment of individual angioedema attacks in the absence of routine prevention while on placebo. Two of the domains with the greatest deficit for patients at baseline versus the general population (bodily pain and social functioning) showed the greatest benefit after routine prevention with C1 INH-nf.

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