Safety and Efficacy of Prophylactic Nanofiltered C1-inhibitor in Hereditary Angioedema

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ABSTRACT

OBJECTIVE: Nanofiltered C1-inhibitor (C1INH-nf) is approved for prophylactic treatment of hereditary angioedema. This study assessed the efficacy and safety of C1INH-nf as prophylactic therapy in a large cohort of patients with hereditary angioedema.

METHODS: An open-label multicenter extension study was performed involving 146 subjects with hereditary angioedema who were treated with C1INH-nf for up to 2.6 years in centers throughout the United States. Subjects were to be treated with C1INH-nf 1000 units every 3 to 7 days. The primary efficacy variable was the number of attacks of angioedema experienced.

RESULTS: Subjects experienced a 93.7% reduction in attacks while taking prophylactic C1INH-nf (0.19 attacks per month; interquartile range, 0.00-0.64) compared with the historical rate of attacks. Some 87.7% reported an attack frequency of 1 or less attack per month during prophylactic C1INH-nf and 34.9% had no attacks during the study. Some 7.5% of subjects experienced relatively frequent attacks despite twice-weekly C1INH-nf. Although twice-weekly dosing was highly effective in most subjects, once-weekly dosing provided adequate control in a subgroup of subjects. No clinical characteristics predicted the response to prophylactic C1INH-nf, including historical attack frequency. C1INH-nf was well tolerated.

CONCLUSION: Prophylactic C1INH-nf is highly effective and safe, and provides durable prophylaxis in the majority of patients with hereditary angioedema. The recommended dose of C1INH-nf 1000 units twice weekly is supported by this open-label study. Individual patients may benefit from further dose adjustment on the basis of response to therapy and individual treatment goals.

KEYWORDS: C1 inhibitor; Concentrate; Hereditary angioedema; Prophylaxis; Therapy
edema and was approved recently in Europe for the acute treatment, prevention, and preprocedural prevention of hereditary angioedema attacks. The prophylactic prevention indication was based on a 22-subject crossover trial in which subjects with relatively severe hereditary angioedema (history of ≥2 attacks per month) were given C1INH-nf or placebo twice per week for 12 weeks and then crossed over to the alternative agent for a subsequent 12 weeks.13 During the placebo period, subjects had a mean of 12.7 attacks, and this was reduced to 6.3 attacks during C1INH-nf treatment (P < .001). Although the end point was robust, this trial was relatively small and of short duration.

We performed an open-label study of prophylactic C1INH-nf to better understand its long-term use in hereditary angioedema. The current report provides the results of prophylactic C1INH-nf treatment in 146 subjects with hereditary angioedema who were treated for up to 2.6 years. The results show that prophylactic C1INH-nf is highly effective and safe in the treatment of hereditary angioedema.

MATERIALS AND METHODS

This was an open-label, single-arm multicenter study to evaluate the efficacy and safety of C1INH-nf for the prevention of hereditary angioedema attacks (NCT01005888). The study was approved by the institutional review board for each participating site. The trial was conducted and data were collected by investigators at each of the participating centers. Laboratory and clinical data were collected with the help of a contract research organization (INC Research, Inc, Charlottesville, Va). Data analysis was performed by the authors.

Eligibility

Patients aged 1 year or more with a known diagnosis of hereditary angioedema who had a history of at least 1 angioedema attack per month or of any laryngeal angioedema were eligible. Patients were excluded if they had a history of allergic reaction to C1INH or blood products, had participated in another (not sponsored by ViroPharma Inc) clinical trial within 30 days of enrollment, or had received another blood product within 60 days of enrollment. All subjects signed written informed consent before participating.

Nanofiltered C1-Inhibitor

The C1INH-nf concentrate used in this study was prepared by Sanquin (Amsterdam, Netherlands) from plasma obtained in the United States.

Study Design

Subjects received prophylactic injections of C1INH-nf (1000 units) at the study site. The suggested dose of C1INH-nf was 1000 units every 3 to 7 days. Subjects had laboratory studies performed every 3 months while in the study. Subjects were asked to keep a daily diary of symptoms. Study personnel collected data about breakthrough attacks or adverse events at each visit. All angioedema attacks were eligible for treatment with open-label C1INH-nf (1000 units, with a second dose 60 minutes later if needed).

The primary efficacy variable recorded for each subject was the number of angioedema attacks. Safety was evaluated by the number and severity of adverse events, and changes in clinical laboratory values (viral serology performed every 3 months) and vital signs.

Complement Testing

Serum for measurement of C1INH antigen/function and C4 level was drawn both immediately before and 60 minutes after the first injection of prophylactic C1INH-nf and every 12 weeks thereafter. Assays were performed by Specialty Laboratories (Valencia, Calif).

Statistics

Results are reported as mean ± standard deviation or median with interquartile range (IQR). Statistical analysis of differences between groups was performed using the Wilcoxon signed-rank test. Bivariate regressions were analyzed by analysis of variance. A $P$ value of less than .05 was considered statistically significant. Statistical analyses were performed using JMP 9 (SAS Institute, Inc, Cary, NC). Unless specified otherwise, the entire cohort of 146 subjects was used for all analyses.

RESULTS

Demographics

A total of 146 subjects received prophylactic C1INH-nf. The mean ± standard deviation age of the subjects was 36.5 ± 16.5 years (range, 3-82 years). Twenty-three subjects were aged less than 18 years. The majority were female (112 of 146, 76.7%) and white (121, 82.9%).

The median (IQR) historical attack rate was 3 (2-4) attacks per month, with a range of 0.08 to 28. Five subjects (3.4%) had a historical attack frequency of less than 1 attack per month. Sixteen of the 22 subjects in the previous randomized prophylactic trial participated in the open-label extension study. None of the 6 subjects who did not participate in this study had experienced an in-

CLINICAL SIGNIFICANCE

- Prophylactic C1INH-nf therapy twice per week was highly effective, durable, and safe in the majority of patients with hereditary angioedema.
- Hereditary angioedema seemed to be well controlled with once per week dosing in many patients.
- Hereditary angioedema was not well controlled in a relatively small fraction of the patients even at twice per week dosing.
crease in attacks while randomized to C1INH-nf, and as a group these 6 demonstrated a 59% decrease in overall attacks, which is slightly more favorable than in the entire group.

Sixty-seven subjects (45.9%) did not complete the study—40 transitioned to commercial C1INH-nf, 3 transferred to another ViroPharma Inc C1INH-nf study, 2 withdrew because of logistic difficulties, 1 transferred to another C1INH drug, 8 withdrew consent, 10 were lost to follow-up, 1 was withdrawn by an investigator, and 2 died.

Impact of Prophylactic Nanofiltered C1-Inhibitor on Angioedema Attacks

The frequency of hereditary angioedema attacks was significantly decreased during treatment with prophylactic C1INH-nf compared with the historical rate at screening ($P < .001$). The median frequency of hereditary angioedema attacks during the study was 0.19 attacks per month (IQR, 0.00-0.64), a 93.7% reduction from the baseline median frequency of 3 (IQR, 2-4). The mean frequency of hereditary angioedema attacks during the study was 0.47 ± 0.83, a 90.0% reduction from the historical mean frequency of 4.7 ± 5.2 attacks per month. The median frequency of attacks during the study in the 67 subjects who did not complete the study was 0.12 (IQR, 0.00-0.74) attacks per month.

Variability in the Response to Prophylactic Nanofiltered C1-Inhibitor

Substantial differences in efficacy were seen within the study population. Fifty-one subjects (34.9%) reported no attacks during the study, and 128 subjects (87.7%) reported 1 attack or less per month during the study. In contrast, 18 subjects (12.3%) reported more than 1 attack per month during the study. Although 18 subjects had an overall attack rate of more than 1 per month on C1INH-nf, only 4 subjects (2.7%) failed to achieve an attack rate of 1 or less per month when treated with C1INH-nf at the recommended twice per week schedule. The other 14 subjects had 1 or less attack per month while receiving twice-weekly dosing ($n = 10$) or were not treated with twice-weekly dosing for at least 30 days ($n = 4$).

No significant correlation was found between monthly attack frequency while using C1INH-nf and either reported historical attack frequency ($R = 0.0016, P = .93, \text{Figure 1A}$) or duration in the study ($R = -0.022, P = .64, \text{Figure 1B}$) (Table 1).

Age and ethnicity had no impact on treatment monthly attack rate ($P = .51$ and $P = .41$). The median monthly attack frequency on C1INH-nf was 0.19 in both males (IQR, 0.00-0.46) and females (IQR, 0.00-0.67); $P = .56$. There was no difference between the historical monthly rate of attacks in male (5.70 ± 6.80) and female (4.43 ± 4.65) subjects ($P = .45$).

Complement testing was performed in 140 subjects. The baseline C1INH functional activity was significantly correlated with the attack frequency during the study ($R = 0.22; P = .01$), with lower baseline C1INH function predicting a higher attack rate during prophylactic C1INH-nf treatment. No significant relationships were seen between the attack frequency during the study and preinjection C1INH antigen ($R = 0.15; P = .09$), preinjection C4 ($R = 0.13; P = .12$), or postinjection C1INH function ($R = 0.09; P = .31$).
Exposure to 17α-Alkylated Androgens

At enrollment, 42 subjects (28.8%) were taking regular prophylactic androgens. During the study, 23 subjects (54.8%) discontinued androgens, 6 subjects (14.3%) discontinued regular use and switched to as-needed use, 5 subjects (11.9%) reduced the androgen dose, and 8 subjects (19.0%) remained on the same dose.

The median monthly attack rate in the 23 subjects who discontinued androgens went from 3.00 (IQR, 1.25-11.00) on androgens to 0.00 (IQR, 0.00-0.31) on prophylactic C1INH-nf. Nine subjects not taking androgens at entry were prescribed androgens during their participation in the study. Of these, 5 subjects were prescribed androgens for short-term prophylaxis and 4 subjects were started on regular androgens.

Frequency of Prophylactic Nanofiltered C1-Inhibitor Administration and Efficacy

Subjects received their C1INH-nf injections at intervals ranging from 1 to more than 14 days. Table 2 shows the rate of angioedema attacks in all subjects at differing intervals. The rate of attacks was highly correlated ($R = 0.911, P < .001$) with the interval between injections (Figure 2A).

Overall, the 146 subjects received 10,618 C1INH-nf injections during the study, of which 90.0% (9542) were given at intervals of approximately twice per week (every 2-4 days) or once per week (every 6-7 days). Dosing interval decisions were made by the subjects and their physicians, and many subjects varied their dosing intervals during the course of the study. Seven subjects received C1INH-nf exclusively twice per week for a median duration of 85 days (IQR, 65-221). Twenty-three subjects received C1INH-nf exclusively once per week for a median duration of 189 days (IQR, 79-246). A total of 116 subjects received C1INH-nf injections at both twice weekly and weekly intervals for a median duration of 289 days (IQR, 191-532). Overall, subjects averaged 1.4 injections per week throughout the study period.

We compared the efficacy of prophylactic C1INH-nf injections for preventing breakthrough angioedema attacks at dosing intervals of 2 to 4 days versus 6 to 7 days. A total of 7247 injections were given at intervals of 2 to 4 days to 123 subjects, accounting for 24,473 study days. During these periods, subjects experienced 185 attacks, or 1 attack for every 132 days of treatment. A total of 2295 injections were given at intervals of 6 to 7 days to 138 subjects.
accounting for 15,654 study days. During these periods, subjects experienced 338 attacks, or 1 attack for every 46 days of treatment.

Because the response to treatment was not uniform between different subjects, we assessed the likelihood of a favorable response at these 2 regimens. A favorable response was defined as having 1 or less attack for the duration of various treatment periods. We analyzed periods between 30 and 120 days. Twice-weekly dosing with C1INH-nf resulted in a favorable response rate that varied from 95.7% at 30 days (88/92) to 70.7% at 120 days (41/58). Once-weekly dosing resulted in a favorable response rate that varied from 69.3% at 30 days (79/114) to 45.7% at 120 days (37/81). Twice-weekly dosing had a more favorable response rate than once-weekly dosing at each interval examined (Figure 2B).

Pharmacokinetics
C1INH-nf increased antigenic and functional C1INH activity 1 hour after administration (mean increase in C1INH antigen of 5.6 to 8.4 mg/dL in subjects aged ≥ 18 years and 6.7 to 15 mg/dL in subjects aged < 18 years).

Safety
Treatment-emergent adverse events reported during the open-label study were analyzed. No subjects discontinued the study drug because of an adverse event. Eighty-six percent of treatment-emergent adverse events were of mild or moderate intensity. Two deaths (not study drug related) were reported. One subject died of pulmonary arterial embolization of foreign material from intravenous injection of an oral medication, and 1 subject died of worsening of pre-existing hepatocellular carcinoma. A total of 99 of 101 serious adverse events reported were considered not related to C1INH-nf, and 2 serious adverse events (musculoskeletal chest pain and major depression) were of unknown relationship. Five subjects (all with underlying risk factors for thrombotic events) experienced serious adverse events of a thromboembolic nature (myocardial infarction, deep vein thrombosis, cerebrovascular accidents [x2] and pulmonary embolism), but none were considered study drug related.

Viral sero-vigilance revealed no evidence of transmission of hepatitis B or C virus, or human immunodeficiency virus. No subjects had clear evidence of a new parvovirus B19 infection during the study.

No severe hypersensitivity reactions related to C1INH-nf were seen. One subject experienced anaphylaxis to shellfish ingestion. No evidence of anti-C1INH antibodies was detected during this study.

DISCUSSION
Management of hereditary angioedema often involves long-term prophylaxis. Androgen and antifibrinolytic drugs have been the mainstay of long-term prophylaxis for many years;4-6 however, potential side effects have made these agents increasingly less desirable to many patients and physicians.8-12,14 C1INH-nf was approved recently in the United States and Europe; however, more needs to be learned about the use of this therapy in clinical practice. Waytes et al15 demonstrated a 60% decrease in angioedema symptoms in 6 subjects with hereditary angioedema who received prophylactic treatment with vapor-heated C1INH every 3 days for 17 days compared with placebo. More recently, Zuraw et al13 reported that C1INH-nf (1000 units twice/week) reduced angioedema attacks in 22 subjects with hereditary
angioedema by 50.8% (from 4.24 attacks/month to 2.09 attacks/month) during a 24-week crossover study.

We now report the results of prophylactic C1INH-nf in 146 subjects with hereditary angioedema taking this medication for a median duration of 248 days (range, 173-507). Relative to the reported median frequency of 3 (range, 2-4) angioedema attacks per month at screening, subjects experienced a 93.7% reduction in attacks while taking prophylactic C1INH-nf (0.19 [IQR, 0.00-0.64] attacks/month). The efficacy of prophylactic C1INH-nf did not vary on the basis of the duration of treatment in the study, suggesting that the benefit is highly durable. C1INH-nf was well tolerated, and the safety profile did not suggest any notable associations.

Substantial variability was observed between subjects’ responses to prophylactic C1INH-nf. The majority of subjects (87.7%) reported an attack frequency of 0 to 1 attack per month during prophylactic C1INH-nf, and 51 subjects (34.9%) had no attacks during the study. Eighteen subjects (12.3%) reported more than 1 attack per month during the study; however, only 4 subjects experienced more than 1 attack per month on twice-weekly C1INH-nf. We did not find any clinical characteristics (including historical attack frequency) that predicted the response to prophylactic C1INH-nf (Figure 1).

Baseline C1INH functional activity was significantly inversely correlated with the response to C1INH-nf prophylaxis, suggesting the possibility that those subjects who had the least favorable response might have required a higher dose of C1INH-nf. Otherwise, no significant associations were found between response to C1INH-nf and baseline C1INH antigen, baseline C4, or postinjection C1INH function.

We found a striking relationship between the C1INH-nf injection intervals and the likelihood of having an attack. Although the approved dose of prophylactic C1INH-nf is 1000 units twice per week, the actual intervals ranged from 1 day to more than 2 weeks between injections (Table 2). Best results were seen with twice-weekly dosing (Figure 2), supporting the previously published pivotal study.

Three limitations of the study should be recognized. The study was nonrandomized and open-labeled. The pretreatment attack rate was estimated on the basis of the subject’s historical frequency of attacks at entry. The injection interval was defined as every 3 to 7 days with treatment decisions determined by the investigators on the basis of local convenience and preference.

CONCLUSIONS
This open-label study demonstrates that prophylactic C1INH-nf therapy at the recommended dose of 1000 units twice per week was highly effective, durable, and safe in the majority of patients with hereditary angioedema. We found that hereditary angioedema seemed to be well controlled in many subjects with once-weekly dosing. Hereditary angioedema was not well controlled even at twice-weekly dosing in a relatively small fraction of the subjects; whether these subjects would benefit from a higher dose per injection was not addressed in this study. Individual patients may benefit from further dose optimization based on response to therapy and individual preference.

Hereditary angioedema is associated with substantial risk of morbidity and mortality. Successful prophylaxis provides considerable psychologic benefit and can prevent emergency visits with the resultant morbidity and loss of opportunity that accrue from having repeated attacks. On the basis of these considerations and the results in this study, we suggest that prophylactic C1INH-nf should be considered in any patient with hereditary angioedema who requires or desires prophylactic treatment.

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References


