

Nanofiltered C1 esterase inhibitor (human) for hereditary angioedema attacks in pregnant women

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ABSTRACT

Data are limited on hereditary angioedema (HAE) in pregnant women and the safety and efficacy of therapies for treatment and prevention of HAE attacks during pregnancy. Prospective studies are unlikely given the rarity of HAE and ethical considerations regarding enrollment of pregnant female subjects in clinical trials. A retrospective analysis of clinical trial and compassionate-use data was conducted to identify subjects who received nanofiltered C1 esterase inhibitor (C1 INH-nf; human) during pregnancy. This study evaluates the efficacy and safety of human C1 INH-nf for treatment and prevention of HAE attacks in pregnant women. Data from pregnant subjects enrolled in either open-label extensions of two randomized, double-blind, placebo-controlled trials of C1 INH-nf or in a compassionate-use program were retrospectively analyzed for efficacy (e.g., total attacks, attack frequency during prophylaxis, and monthly attack rates) and safety (e.g., pregnancy outcomes and adverse events). C1 INH-nf was administered as acute treatment, preprocedural prophylaxis, or routine prophylaxis. C1 INH-nf prophylaxis substantially reduced monthly attack rates. Of 16 subjects, 13 delivered 14 healthy neonates (1 set of twins). Two adverse fetal outcomes were reported; neither was considered by the principal investigator to be related to C1 INH-nf. One subject's pregnancy outcome was unknown. This analysis shows a favorable risk–benefit profile for C1 INH-nf for managing HAE during pregnancy. NCT Identifier: NCT00438815; NCT00462709.

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Hereditary angioedema (HAE) is a rare disorder caused by decreased or dysfunctional expression of C1 esterase inhibitor (C1 INH).^{1–6} This deficiency in functional C1 INH results primarily from an autosomal dominant inheritance of C1 INH gene mutations, with 25% of cases caused by spontaneous mutation.³

HAE is characterized by recurrent episodic attacks of nonpruritic subcutaneous or submucosal edema, which may involve the face, extremities, gastrointestinal tract, genitalia, or upper airway.^{2,4,7} Although attacks are not typically life-threatening, with the exception of upper airway angioedema, which can lead to

obstruction and asphyxiation if untreated,^{4,7,8} HAE can cause significant pain, reduced physical and social functioning, and reduced health-related quality of life.^{9,10} HAE attacks often occur spontaneously but may be triggered by mechanical trauma from medical procedures or surgery, infection, repetitive motion, or stress.^{7,11–13} Fluctuations in levels of sex hormones associated with puberty, menses, pregnancy, and oral contraceptive or hormone-replacement therapy use may also precipitate attacks.^{14–19} Generally, women with HAE experience more severe and more frequent attacks than men.^{9,14,19}

Because HAE is an extremely rare disease and because ethical considerations preclude most prospective studies in pregnant women, data on the effect of HAE on pregnancy or on the safety and efficacy of novel therapeutic options for the treatment and prevention of HAE attacks in pregnancy are limited. The majority of available information is based on retrospective analyses and case reports with small numbers of pregnant patients. HAE has not been shown to affect rates of pregnancy or spontaneous abortion in women of childbearing age.¹⁷ The highly variable effect of pregnancy on frequency of attacks suggests that sex hormones during pregnancy have varying effects on endogenous C1 INH production and regulation of bradykinin.^{16,17,20–22} HAE attacks occur much less frequently during delivery than during pregnancy.^{17,21,23} Vaginal delivery is not considered a major risk factor for attacks¹⁷ neither is cesarean delivery *per se*; however, surgical trauma of tissues is a potential attack trigger.

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Table 1 Consensus guidelines for pregnant women with hereditary angioedema

Medication	Recommendation	Notes	Reference
Attenuated androgens	Contraindicated	Although contraindicated, there is a recommendation for situations in which short-term prophylaxis is required and C1 INH is not available. In such cases, only during the third trimester of pregnancy may attenuated androgens be considered as short-term prophylactic therapy	Bowen <i>et al.</i> ¹ ; Gompels <i>et al.</i> ²³
C1 INH	Use as needed	May be used for routine prophylaxis in severe cases. It is recommended that C1 INH be readily available for patients undergoing medical procedures or considered for preprocedural prophylaxis as needed	Bowen <i>et al.</i> ¹ ; Gompels <i>et al.</i> ²³
Tranexamic acid	Use with caution	Excreted in breast milk	Gompels <i>et al.</i> ²³

Source: Refs. 1 and 23.

C1 INH = C1-esterase inhibitor.

Guidelines for HAE treatment advise against anesthesia by endotracheal intubation for cesarean delivery and recommend having C1 INH available.^{1,23}

Approaches to HAE management include acute treatment, short-term (*e.g.*, preprocedural) prophylaxis, and routine prophylaxis. Guidelines recommend C1 INH for treatment and prophylaxis of HAE during pregnancy (Table 1),^{1,23} based largely on successful C1 INH use during pregnancy as documented in case reports, observational studies, and a large retrospective survey.^{13,21,22,24} C1 INH prophylaxis is also recommended during labor for women whose attacks have increased in severity and/or frequency during pregnancy.¹⁶

Nanofiltered C1 INH (C1 INH-nf; human; Cinryze; ViroPharma, Inc., Exton, PA) is approved in the United States for routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE.²⁵ Cinryze is approved in the European Union for treatment and preprocedure prevention of angioedema attacks in adults and adolescents with HAE.²⁶ It is also approved in the European Union for the routine prevention of angioedema attacks in adults and adolescents with severe and recurrent attacks of HAE who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment.²⁶ Currently available oral prevention therapies are contraindicated in pregnancy^{1,23}; thus, C1 INH-nf seems a suitable treatment option. The objective of this analysis was to test this supposition by evaluating clinical trial

and compassionate-use data available for subjects who received C1 INH-nf during pregnancy. Some of these data were presented at the 2009 annual meeting of the American Academy of Allergy, Asthma, and Immunology²⁷ and the 2010 annual meeting of the American College of Allergy, Asthma, and Immunology.²⁸

METHODS

This retrospective analysis of C1 INH-nf use during pregnancy evaluates data from open-label extension studies of two randomized, double-blind, placebo-controlled trials²⁹ and from a compassionate-use program. The first open-label extension studied C1 INH-nf as acute treatment for HAE attacks with optional preprocedural prophylaxis (LEVP 2006-1)³⁰; the other studied C1 INH-nf as routine prophylaxis for prevention of HAE attacks with optional acute treatment if needed (LEVP 2006-4).³¹ The protocols were approved by each site's Institutional Review Board, and all subjects provided written informed consent.

Pregnancy was an exclusion criterion for both pivotal, randomized, placebo-controlled trials but was allowed in the open-label extensions. No *a priori* formal analysis was planned for evaluating efficacy and safety of C1 INH-nf in pregnant subjects. Women who were pregnant or became pregnant during the studies were identified retrospectively. Information was collected from case report forms, severe adverse event (AE) reports collected through the Pharmacovigilance system (rather than standard protocol reporting), monitoring

logs, and direct correspondence with investigators. Poststudy follow-up yielded the dates and outcomes of the pregnancies. Knowledge of these dates allowed the partition of data into intervals labeled “pregnant” and “not pregnant.”

The dosing regimens from the two studies were as follows. For acute treatment, C1 INH-nf at 1000 U was administered i.v. followed by a second 1000-U dose 60 minutes later, if necessary. Subjects could be treated for multiple attacks. Preprocedural prophylaxis consisted of C1 INH-nf at 1000 U within 24 hours of a surgical or dental procedure if necessary. For routine prophylaxis, C1 INH-nf at 1000 U was given every 3–7 days. In the compassionate-use program, patients received C1 INH-nf at 1000 U twice weekly for prophylaxis.

Efficacy assessments in this analysis of C1 INH-nf use in pregnancy included dosing data, total number of attacks during pregnancy versus historical attack rates, and frequency of attacks during prophylactic treatment. Subjects received diary cards to record all attacks on a daily basis; historical attack rates were provided by subjects (anamnestic reports). Safety assessments included pregnancy outcomes, viral safety testing (hepatitis B virus, hepatitis C virus, human immunodeficiency virus, and parvovirus), and testing for antibodies to C1 INH. Treatment-emergent AEs were summarized and relation of AEs to study drug was recorded.

Given the lack of a control group, formal statistical analyses were not performed. All data summaries are descriptive.

RESULTS

Study Population

A total of 16 unique subjects received C1 INH-nf for HAE treatment or prophylaxis during pregnancy: 2 subjects from the acute treatment study (LEVP 2006-1), 11 subjects from the routine prophylaxis study (LEVP 2006-4), and 2 subjects who were enrolled in both open-label extensions. One additional subject received C1 INH-nf in a compassionate-use program. The mean age was 26 years (range, 16–45 years). All ages reported are ages at conception.

Acute Treatment Study (LEVP 2006-1)

Two subjects enrolled in this open-label extension with optional preprocedural prophylaxis received C1 INH-nf doses during their pregnancy as preprocedural prophylaxis associated with labor and delivery (Table 2). One subject (17 years old) received 1 dose as prophylaxis 1 day before her delivery date. Her historical attack rate was one attack per month. The subject was enrolled in the study for the last ~10 weeks (69 days) of her pregnancy and she experienced no attacks dur-

ing this period. She delivered a full-term healthy male infant.

The other subject (22 years old) received 1 dose as prophylaxis on her delivery date. Her historical attack rate was four attacks per month. During the three trimesters of her pregnancy while enrolled in this study, she did not experience any attacks and delivered a full-term healthy male infant.

Prophylaxis Study (LEVP 2006-4)

Eleven subjects received prophylactic C1 INH-nf during pregnancy and their data are listed in Table 2. The number of doses administered ranged from 2 to 83 (data unknown for one subject). Most of the subjects experienced a lower attack rate on C1 INH-nf therapy (Table 2). Three subjects experienced attacks while pregnant but had fewer attacks on C1 INH-nf therapy versus their historical rates. One subject experienced 1 attack during 122 days, another experienced 4 attacks during 253 days, and the third subject experienced 11 attacks during 267 days of prophylactic treatment. Six subjects experienced no attacks while receiving routine prophylaxis. Outcomes for two subjects were unknown.

Eight subjects delivered nine healthy neonates (one set of twins; Table 2). One subject with a history of miscarriage and ectopic pregnancy experienced a spontaneous abortion. This adverse fetal outcome was considered unrelated to C1 INH-nf by the investigator. One subject received 34 doses (32 for prophylaxis, 2 as acute treatment) beginning at week 17 of her pregnancy. The subject delivered a stillborn infant with multiple congenital anomalies. The anomalies were detected at week 23 of the pregnancy and considered unrelated to C1 INH-nf by the investigator because the anomalies would have predated C1 INH-nf use. Thus, this adverse fetal outcome could not have been related to C1 INH-nf. One subject was lost to follow-up, and the infant outcome is unknown.

Both Studies (Acute Treatment and Prophylaxis; LEVP 2006-1 and LEVP 2006-4)

Two subjects in both open-label extensions (acute treatment and prophylaxis) received C1 INH-nf during their pregnancy (Table 2). One subject was 33 years old and received 25 doses of C1 INH-nf (3 for prophylaxis and 22 as acute treatment) during the first two trimesters of her pregnancy. Her historical attack rate was 3 to 4 attacks per month. The subject experienced 19 unique attacks; 16 occurred while enrolled in the acute treatment study and 3 occurred in the 3 weeks during which she was also enrolled in the prophylaxis study. Information regarding this subject's attacks is listed in Table 2; however, the ability to accurately assess her monthly attack rate on C1 INH-nf treatment is limited

Table 2 Characteristics of C1 INH-nf usage, HAE attacks, and infant outcomes in pregnant subjects

Regimen	Subject Age at Conception (yr)	Historical Monthly Attack Rate	Monthly Attack Rate on C1 INH-nf during Pregnancy	Average No. of C1 INH-nf Doses per Week	Dates (trimester[s]*) of exposure to C1 INH-nf	Infant Outcome	Additional Details
Acute treatment	22	4	0	NA#	January 20, 2008 to March 18, 2009 (NA#)	Healthy, full-term	7 lb, 13 oz; 19.5 in; delivered March 18, 2009
Acute treatment	17	1	0	NA\$	January 14, 2008 to February 11, 2009 (3\$)	Healthy, full-term	8 lb, 4 oz, 20.5 in; delivered January 15, 2008
Prophylaxis	33	4	0.5	2.1	March 19, 2007 to March 31, 2009 (1, 2, and 3)	Healthy	Delivered November 26, 2007
Prophylaxis	16	2	1.3	2.2	November 30, 2007 to March 23, 2009 (1, 2, and 3)	Healthy, full-term	6 lb, 6 oz; 20.5 in; delivered March 6, 2009
Prophylaxis	32	2	0	2	July 30, 2008 to March 10, 2009 (1, 2, and 3)	Healthy, full-term	Delivered March 18, 2009
Prophylaxis	19	3	0	1.5	September 5, 2008 to February 6, 2009 (1, 2, and 3)	Healthy, full-term	9 lb, 5 oz; 19.5 in; delivered March 26, 2009
Prophylaxis	29	4	0	1.8	September 25, 2008 to March 31, 2009 (1, 2)	Healthy, full-term	6 lb, 5 oz; 18.5 in; delivered August 6, 2009
Prophylaxis	26	2	0	1.1	October 17, 2007 to March 30, 2009 (2 and 3)	Healthy	Delivered January 30, 2008
Prophylaxis	21	16	0.2	2	September 25, 2008 to March 30, 2009 (2 and 3)	Stillborn¶	—
Prophylaxis	20	2	Unknown	Unknown	March 6, 2007 to March 13, 2007 (1)	Unknown	—
Prophylaxis	45	2–3	0	2.1	March 6, 2007 to March 30, 2009 (1)	Spontaneous abortion¶	—
Prophylaxis	29	2	0	1.2	June 24, 2008 to February 10, 2009 (3)	Healthy twins	Baby 1 = 6 lb, 8 oz; Baby 2 = 5 lb, 2 oz; delivered July 22, 2008
Prophylaxis	32	12	Unknown	Unknown	March 8, 2007 to May 21, 2007 (unknown)	Healthy	—

Table 2 Continued

Regimen	Subject Age at Conception (yr)	Historical Monthly Attack Rate	Monthly Attack Rate on C1 INH-nf during Pregnancy	Average No. of C1 INH-nf Doses per Week	Dates (trimester[s]*) of exposure to C1 INH-nf	Infant Outcome	Additional Details
Acute treatment and prophylaxis	23	.33	Acute treatment, 1.3; prophylaxis, 0	1.1	Acute treatment, January 25, 2007 to November 13, 2008; prophylaxis, November 20, 2008 to March 31, 2009 (1, 2, and 3)	Healthy, full-term	8 lb, 8 oz; 19 in; delivered March 23, 2009 (cesarean delivery); received C1 INH-nf at 1000 U before delivery
Acute treatment and prophylaxis	33	3–4	4.4**	1.3**	January 25, 2007 to June 4, 2007** (1 and 2)	Healthy	C1 INH-nf started early in pregnancy; transitioned to another plasma-derived C1 INH product before delivery; cesarean delivery without complication
Compassionate use	25	6–10	Unknown	2	May 11, 2006 to April 13, 2007 (3)	Healthy	8 lb, 5 oz; 21 in; delivered on June 19, 2006

*Trimesters of exposure are based on estimated conception dates.

#Subject only received 1 dose prior to cesarean delivery although she participated in the study for the full duration of her pregnancy.

§Subject only received 1 dose during pregnancy.

¶Considered unrelated to C1 INH-nf treatment by the investigators because of evidence supporting other causes for the adverse fetal outcomes, such as early congenital abnormalities and history of miscarriage and ectopic pregnancy.

||The average weekly dose listed is the average dose received during the prophylaxis study (November 20, 2008 to March 23, 2009). Before enrollment into the prophylaxis study, the subject received 6 acute treatment doses and 1 preprocedural prophylactic dose during the 114 days of her participation in the acute treatment study (July 23, 2008 to November 13, 2008).

**Enrollment in the acute treatment and prophylaxis studies overlapped. The calculated average weekly dose of 1.3 doses/week reflects the combined acute treatment and prophylaxis study dosing data due to the overlap in study periods. Monthly attack rate on C1 INH-nf during pregnancy reflects the total number of attacks from both studies (total of 19 unique attacks) because of the overlap in time frames. Specifically, the subject experienced four attacks during the acute treatment study from January 25, 2007 to February 21, 2007, for which she received 6 doses of C1 INH-nf. She then experienced three attacks during the prophylaxis study from February 22, 2007 to March 13, 2007 (20 days). She received 7 doses of C1 INH-nf during this time, 4 as acute treatment and 3 as prophylaxis (on days 1, 5, and 15). Finally, she experienced 12 attacks, again in the acute treatment study from March 14, 2007 to June 4, 2007, for which she received 12 doses of C1 INH-nf. C1 INH-nf = nanofiltered C1-esterase inhibitor; HAE = hereditary angioedema; NA = not applicable.

by the overlap in study periods and relative lack of data. She delivered a healthy female infant.

The other subject was 23 years old and received 26 doses of C1 INH-nf (20 for prophylaxis and 6 as acute treatment) during her pregnancy. Before enrollment, her historical attack rate was 0.33 attacks per month and increased during pregnancy to ~1.3 attacks per month; she received acute treatment for each attack. She then received routine prophylaxis for the remainder of her pregnancy and experienced no additional attacks. She delivered a full-term healthy female infant.

Compassionate-Use Program

The subject was 25 years old and received an estimated 12 doses of C1 INH-nf (based on the compassionate-use dosing regimen and available exposure data) during the last 5 weeks of her third trimester (Table 2). Her historical attack rate was 6–10 attacks per month. Although this subject's attack rate while on C1 INH therapy was not documented, it is noteworthy that she delivered a healthy male infant.

Safety

In the subjects from the two open-label trial extensions, the most commonly reported treatment-emergent AEs were infection (*e.g.*, upper respiratory infections, nasopharyngitis, urinary tract infection, sinusitis, and candidiasis), gastrointestinal disorders (*e.g.*, nausea, vomiting, constipation, abdominal pain, and diarrhea), headache, and rash. No serious AEs were considered drug related by the investigators and no clinically relevant antibodies to C1 INH were detected. There was no evidence of viral transmission related to C1 INH-nf exposure. No AEs were reported in the compassionate-use program.

COMMENT

There are numerous HAE management considerations for women who are pregnant or trying to become pregnant. Whether initiating therapy or modifying a patient's existing regimen for acute and/or prophylactic treatment of HAE, clinicians are faced with balancing the needs and safety of the mother and potential effects of drug exposure to the fetus.

Consensus recommendations for pregnant women with HAE (Table 1) differ from those for the general patient population. Attenuated androgens, commonly used for prevention of HAE attacks, carry potential side effects that may complicate conception (*e.g.*, amenorrhea and menstrual irregularities) and are contraindicated in pregnancy (category X).^{1,23,32,33} Tranexamic acid, a fibrinolytic used to treat HAE, crosses the placenta and is excreted in breast milk; accordingly, use during pregnancy and breastfeeding must be approached with caution.³⁴ C1 INH is considered to be

the safest option for prophylactic therapy in pregnant patients with HAE and may be used as needed for acute treatment as well.^{1,23} An infusion of C1 INH may be warranted around the time of delivery,²³ especially for patients who experienced a higher frequency and/or more severe attacks during pregnancy.¹⁶ Although HAE attacks do not often complicate normal vaginal delivery,²³ the consequences of an attack during delivery could be serious and merit discussion between the patient and obstetrician regarding the need for C1 INH. For cesarean deliveries, a C1 INH infusion administered beforehand may prevent an attack precipitated by surgical (tissue) trauma, and guidelines recommend regional anesthesia to avoid triggering a laryngeal attack.²³

HAE and its impact on a patient may worsen during pregnancy, and the risk of attacks may be higher during the postpartum period.^{16,17,23} The associated physical pain, anxiety, depression, reductions in health-related quality of life, and physical and social functioning^{9,10} may be exacerbated in HAE patients who are pregnant or nursing and therefore potentially limited in their use of medications, such as painkillers, antidepressants, and anxiolytics. Abdominal HAE attacks may cause clinically significant hypotension; increase the risk of dehydration; and cause pain, nausea, and vomiting that can compromise patient nutrition or the ability to breastfeed.^{4,9,20,23} It is important that HAE be adequately managed during pregnancy and breastfeeding to reduce the intrinsic burden that HAE may place on maternal bonding and childcare and to help ensure the health and well-being of mother and child.

In this retrospective analysis of pregnant subjects identified from two open-label studies on C1 INH-nf for treatment and prevention of HAE attacks and a compassionate-use program, C1 INH-nf appeared to be safe in the treatment and prevention of attacks during pregnancy and delivery. Duration of exposure of the fetus to C1 INH-nf ranged from 1 day to a full pregnancy term, which reflects diverse clinical scenarios. Substantial reductions in monthly HAE attack rates were observed for most women receiving C1 INH-nf prophylaxis (Table 2). Of the 16 unique subjects, 13 subjects delivered 14 healthy neonates (including 1 set of twins), 2 subjects had adverse fetal outcomes deemed unrelated to C1 INH-nf by investigators, and 1 subject's outcome was unknown. In both cases of adverse fetal outcomes, there was convincing evidence supporting other causes, such as early congenital abnormalities that would have predated C1 INH-nf therapy and history of miscarriage and ectopic pregnancy. There was no evidence of viral transmission related to C1 INH-nf exposure or detection of clinically relevant antibodies to C1 INH.

This study is limited by its retrospective nature, although to perform an *a priori* randomized study on C1 INH in pregnant women would be unethical. Also,

because HAE may worsen during pregnancy and the effect of pregnancy on HAE varies by patient and by trimester, it is not only unethical but also difficult to establish a control or comparator other than the patient herself, before and after initiation of C1 INH-nf therapy. These subjects were enrolled in studies with primary objectives to evaluate C1 INH-nf for prevention or treatment of attacks, not outcomes related to pregnancy, and these data are not generalizable to all pregnant women. Nevertheless, this analysis provides clinically meaningful information on fetal outcomes and contributes to our understanding of HAE and the potential role of C1 INH-nf during pregnancy and delivery. Areas of needed research include the effect of pregnancy on attack frequency, severity, or location as well as potential trends associated with each trimester. It would also be of interest to determine whether prophylaxis with C1 INH-nf facilitated conception compared with other prophylactic treatments. Additionally, an analysis assessing whether C1 INH-nf treatment pre- and postdelivery could reduce attacks during this high-risk time period would be of interest. These research needs in pregnancy underscore the greater severity of HAE for women, which is also reflected by the predominance of women (67–88% of the trial population) enrolled in several studies of C1 INH.^{29,30,35}

Results of this study are consistent with other reports that evaluated the safety and efficacy of C1 INH use in pregnant patients for the prevention^{13,21,24} and acute treatment^{13,21,22,24} of HAE attacks. In a retrospective analysis of 118 pregnancies in 41 patients from the Hungarian National HAE Registry, 13 patients received 91 vials of C1 INH concentrate (500 U) as acute treatment or prophylaxis.²¹ Symptoms consistently improved within 15–60 minutes of administration, and prophylactic treatment successfully prevented additional attacks. All patients whose pregnancies progressed to delivery and who received C1 INH therapy delivered healthy neonates. In an observational analysis of 35 pregnancies in 22 women, C1 INH concentrate (500 or 1000 U) was used for treatment of attacks during 29 pregnancies and was administered prophylactically (~1 hour) before delivery in all 35 pregnancies.²² All attacks were successfully treated with C1 INH; no attacks occurred during delivery. No stillbirths or spontaneous abortions occurred.

Data from this analysis support previously published experience of C1 INH in pregnancy as well as published guidelines, which identify C1 INH as the safest prophylactic agent to use during pregnancy relative to attenuated androgens, which are generally contraindicated, and antifibrinolytics, which are only administered with caution during pregnancy.^{1,23} This retrospective analysis evaluating C1 INH-nf in 16 pregnant women enrolled in open-label extensions of two

studies and a compassionate-use program establishes the favorable risk–benefit profile of C1 INH-nf for HAE management during pregnancy.

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