Safety of recombinant human C1 esterase inhibitor for hereditary angioedema attacks during pregnancy

Dumitru Moldovan, MD, PhD[a,*], Jonathan A. Bernstein, MD[b], Roman Hakl, MD[c], Grzegorz Porebski, MD, PhD[d], Kimberly Poarch, PA-C[e], William R. Lumry, MD[e,f], and Anurag Relan, MD[g]

Clinical Implications

- Limited clinical data are available on hereditary angioedema treatments during pregnancy. A case series of 14 pregnant women demonstrated that treatment with recombinant human C1 inhibitor was generally safe and well tolerated.

TO THE EDITOR:

Hereditary angioedema (HAE) is a rare (<1 in 50,000) genetic disorder characterized by episodes of cutaneous and mucosal angioedema.[1] HAE is caused by insufficient suppression of complement and contact-system cascades due to a deficiency of functional C1 inhibitor (C1-INH).[1] It has been demonstrated that HAE abdominal attacks are more frequent during pregnancy, but there is no consensus on which trimester is most associated with increased attack rates.[2,3] Some data suggest that more severe attacks and symptoms occur during the first trimester,[2] whereas other data suggest a greater number of attacks in the second and third trimesters.[3] Changes in hormone levels during pregnancy may exacerbate HAE attacks, and concerns with administration of certain medications during pregnancy can complicate HAE management.[1-3]

Recombinant human C1-INH (rhC1-INH) is indicated in the United States for the treatment of acute attacks in adolescents and adults with HAE. Data have demonstrated that rhC1-INH is efficacious and well tolerated for the acute treatment of HAE attacks,[4,5] and as prophylaxis in patients with frequent attacks of HAE.[6] However, data are limited on the treatment of HAE attacks in women who are pregnant. The objective of this current communication was to further characterize the clinical outcomes of pregnant patients with HAE who were treated with rhC1-INH to manage HAE attacks, with the intent that these real-world findings will build a knowledge base around the use of rhC1-INH in this patient population.

Identified as part of routine pharmacovigilance or clinical trial participation, pregnant women with HAE from the United States and Europe who received rhC1-INH were followed to term. Adverse events that occurred during pregnancy were assessed and neonatal outcomes were reported.

Fourteen pregnant women aged 17 to 37 years with HAE treated with rhC1-INH were identified (Table I) through spontaneous event reporting to Pharming Group NV (n = 13) or during participation in a Pharming-sponsored clinical trial (n = 1). Two of these 14 patients had an HAE type identified; both had type I HAE. Patient 9 received an unspecified number of treatments for HAE attacks, as well as a 4200-IU dose predelivery as short-term prophylaxis. Patient 12 received rhC1-INH for 24 attacks and received 26 rhC1-INH doses as prophylaxis. Patient 13 received rhC1-INH for 11 attacks and received 1 rhC1-INH dose as prophylaxis. The other 11 patients were treated with rhC1-INH (range, 2100-4200 IU) for 1 (n = 1 patient), 2 (n = 2), 4 (n = 1), 6 (n = 1), 8 (n = 2), 9 (n = 2), 38 (n = 1), or 41 (n = 1) HAE attacks while pregnant. For

TABLE I. Patients' demographic characteristics and HAE attack management

Patient	Age (y)	Weight (kg)	rhC1-INH dose per attacks	No. of treatments	Second rhC1-INH dose required for any attack	Rescue medication required for any attack
Patient 1	27	65.5	2100 IU	9	No	No
Patient 2	NR	72.0	2100-4200 IU	41	No	No
Patient 3	21	84.0	2100 IU	8	No	No
Patient 4	29	120.0	4200 IU	4	No	No
Patient 5	24	NR	2100-4200 IU	1	No	No
Patient 6	30	63.6	50 IU/kg	6	No	No
Patient 7	26	NR	4200 IU	2	No	No
Patient 8	33	NR	50 IU/kg	2	No	No
Patient 9	23	NR	4200 IU	>1*	No	No
Patient 10	20	80-82	4200 IU	9	No	No
Patient 11	25	63	2100-3150 IU†	8	Yes‡	No
Patient 12	37	66	4200 IU	50§	No	No
Patient 13	17	55	2700-4200 IU	12¶	No	No
Patient 14	37	75	4200 IU	38	No	No

NR, Not reported.
*Received rhC1-INH during pregnancy a "few" times and a prophylactic dose of rhC1-INH during delivery.
†Overall, 25,900 IU of rhC1-INH administered during pregnancy.
‡Received an initial dose of 3150 IU for an attack; a second dose (2100 IU) was administered 18 h later when symptoms did not resolve.
§A total of 24 acute treatments and 26 prophylactic treatments (rhC1-INH 3 times weekly).
¶Eleven treatments for HAE attacks and 1 prophylactic treatment.

TABLE II. Additional information on childbirth outcomes

Patient	Delivery method	Outcome
Patient 1	Vaginal	• Gestational age at time of first exposure: ~2 mo • Live birth at 38 wk (2850 g) • Apgar score* = 10 (at 1 and 5 min) • No fetal distress, birth defects, or congenital abnormalities
Patient 2	Vaginal	• Gestational age at time of first exposure: ~1 wk • Live birth at 42 wk (3690 g) • No fetal distress, birth defects, or congenital abnormalities
Patient 3	Cesarean	• Gestational age at time of first exposure: ~19 wk • Live birth at 39 wk (3370 g) • No fetal distress, birth defects, or congenital abnormalities
Patient 4	Vaginal	• Live birth at 42 wk (3370 g) • Apgar score* = 10 (at 1 and 5 min) • No fetal distress, birth defects, or congenital abnormalities
Patient 5	NR	• Live birth • No fetal distress, birth defects, or congenital abnormalities
Patient 6	NR	• Gestational age at time of first exposure: 8 wk • Live birth • No fetal distress, birth defects, or congenital abnormalities
Patient 7	NR	• Live birth • No fetal distress, birth defects, or congenital abnormalities
Patient 8	NR	• Gestational age at time for first exposure: ~16 wk • Live birth at 41 wk • No fetal distress, birth defects, or congenital abnormalities
Patient 9	Cesarean	• Live birth at 41 wk (3480 g) • Apgar score* = 8-9 • No fetal distress, birth defects, or congenital abnormalities
Patient 10	Vaginal	• Gestational age at time of first exposure: 29 wk • Live birth at 41 wk (2700 g) • Apgar score* = 10 • No fetal distress, birth defects, or congenital abnormalities
Patient 11	Vaginal	• Gestational age at the time of first exposure: 14 wk • Live birth at 39 wk (2470 g) • Apgar score* = 10 • No fetal distress, birth defects, or congenital abnormalities
Patient 12	Vaginal	• Gestational age at the time of first exposure: 8-12 wk • Live birth at 38 wk • No fetal distress, birth defects, or congenital abnormalities
Patient 13	Vaginal	• Gestational age at the time of first exposure: 24-25 wk • Live birth at 39 wk • No fetal distress, birth defects, or congenital abnormalities
Patient 14	Vaginal	• Gestational age at the time of first exposure: 4 wk • Live birth at 41 wk • Apgar score* = 8-9 • No fetal distress, birth defects, or congenital abnormalities

NR, Not reported.
*Possible score 0 to 10, with range of 7-10 classified as reassuring.

all attacks reported for the 14 patients, only 1 attack (in patient 11) required more than 1 dose of medication. The attack experienced by this patient occurred at multiple locations (abdomen, urogenital region, and left hand) and was treated with an initial rhC1-INH dose of 3150 IU. When symptoms had not resolved 18 hours later, a second rhC1-INH dose of 2100 IU was administered and resulted in a rapid remission of symptoms.

Regarding anatomical locations of special interest, 10 life-threatening upper airway HAE attacks occurred in 2 patients (patients 3 [facial/laryngeal] and 7 [laryngeal]). Improvement in clinical symptoms was reported for all 10 of these HAE attacks within 2 to 4 hours after rhC1-INH administration. In addition, patient 4 experienced 4 separate facial HAE attacks, each successfully treated with a single rhC1-INH dose, with no additional medication required.

There were no adverse events considered related to rhC1-INH treatment during the pregnancy period; patient 6 experienced an episode of nausea, vomiting, and diarrhea, but it was considered

by the health care provider to be related to a "stomach bug." Of the 14 pregnant women in this case series, birth delivery method details were available for 10. Eight had vaginal deliveries and 2 had cesarean deliveries, all without complications (Table II). All 14 women gave birth at full term to healthy babies.

There are no published clinical studies that compare HAE treatment regimens during pregnancy. However, expert consensus recommends C1 inhibitors as first-line treatment for acute HAE attacks during pregnancy on the basis of its safety profile.[1,7,8] When a C1 INH is unavailable, long-term prophylactic treatment with tranexamic acid could be an option.[1,7] Because data regarding the safety of HAE treatment during pregnancy are limited, icatibant and ecallantide are not recommended for women who are pregnant.[1,7] Attenuated androgens are contraindicated during pregnancy because they have been shown to cross the placenta and may impact fetal development.[1,7] Before the current case series, there was a report of 3 pregnant patients who were treated with a median dose of 4200 IU rhC1-INH for 50 HAE attacks, with time to complete symptom resolution of 17 hours (range, 3-48 hours).[9] One patient had 4 HAE attacks (gastrointestinal and laryngeal, n = 2; gastrointestinal, n = 2) treated with an initial dose of rhC1-INH 4200 IU in which the patient reported temporary improvement in symptoms but required a second treatment (rhC1-INH 4200 IU [n = 3] or icatibant 30 mg [n = 1]) for symptom resolution.[9] All 3 women in that earlier report delivered healthy, full-term infants, with no congenital abnormalities reported.[9]

Safety data for HAE treatments during pregnancy are limited because women who are pregnant are commonly excluded from clinical trials during drug development for ethical reasons. Patients must rely on HAE treatment data from pharmacovigilance, observational studies such as registries, case-control studies, and surveillance methods to establish a knowledge base of treatment and outcomes for pregnant women with HAE. As the knowledge surrounding HAE treatments during pregnancy continues to grow, this information will help women diagnosed with HAE who are pregnant or planning to become pregnant make informed treatment decisions in consult with their health care providers. This review focused on the safety aspects of drug exposure during pregnancy, and there were no apparent dose-related safety findings. Although the series was not intended to evaluate efficacy, there was no evidence for differential efficacy in pregnant versus nonpregnant patients with HAE. In conclusion, we report that treatment with rhC1-INH for HAE attacks in pregnant women was generally safe and well tolerated. All 14 women in this study delivered healthy babies at full term without complications.

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[a]MediQuest Clinical Research, Sangeorgiu de Mures, Romania
[b]University of Cincinnati, College of Medicine, Cincinnati, Ohio
[c]Department of Clinical Immunology and Allergology, St Anne's University Hospital in Brno, Faculty of Medicine, Masaryk University, Brno, Czech Republic
[d]Department of Clinical and Environmental Allergology, Jagiellonian University Medical College, Sniadeckich, Krakow, Poland
[e]Allergy & Asthma Specialists of Dallas, Dallas, Texas
[f]University of Texas Southwestern Medical School, Dallas, Texas
[g]Pharming Healthcare Inc, Bridgewater, NJ
[*]This author is deceased.

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Corresponding author: Jonathan A. Bernstein, MD, University of Cincinnati, College of Medicine, 231 Albert Sabin Way, ML#563, Cincinnati, OH 45267. E-mail: bernstja@ucmail.uc.edu.

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