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C1-INH concentrate for prophylaxis during pregnancy in hereditary angioedema with normal C1-INH



In the *Journal of Allergy and Clinical Immunology: In Practice* article "Use of pdC1-INH concentrate for long-term prophylaxis during pregnancy in hereditary angioedema with normal C1-INH," Garcia et al¹ proposed a study for long-term prophylaxis of hereditary angioedema (HAE) with normal C1-INH in pregnancy. Although it was regarded as the first study for such a protocol, a similar article "Successful perinatal management of hereditary angioedema with normal C1 esterase inhibitor and factor XII mutation using C1 esterase inhibitor therapy" by Gibbons et al² was published in print 6 months earlier in the journal *Annals of Allergy, Asthma, and Immunology* on December 2017. Our publication was available online and 3 days after the listed initial submission to *JACI: In Practice* by Garcia et al. These unique cases resemble the action of 2 ships unknowingly passing each other on a moonless night.

Although both articles display a systematic way to provide plasma-derived C1-INH, their dosage and frequency vastly differ. Garcia et al followed 3 cases of type III HAE and proposed a dose of 1000 International Units (IU) once or twice a week, which greatly reduced the frequency of attacks from once or twice a week to none or once a month. In contrast, the article by Gibbons et al offered a differing dose and frequency for plasma-derived C1-INH. They reported a case in a pregnant woman who had angioedema attacks starting at 16 weeks of pregnancy occurring at a frequency of up to 3 attacks a week. The authors suggested infusions every 3 days. After starting the patient on 1500 IU of

plasma-derived C1-INH prophylactic infusion every 3 days at 24-week gestation, the patient only experienced 4 additional episodes requiring rescue doses of C1-INH.

Both articles describe similar genetics involving mutation of coagulation factor XII along with the possibility of estrogen-mediated angioedema with normal C1-INH quantity and function. The treatment dosage and frequency slightly differ in each article; however, they both demonstrate the value of life-saving plasma-derived C1-INH to reduce or eliminate the threat of angioedema in pregnancy. These articles exemplify the importance of establishing a life-saving protocol for those with type III HAE.

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Reply



To the Editor:

Hereditary angioedema (HAE) is clinically characterized by recurrent cutaneous and mucosa angioedema induced by over-concentration of bradykinin in tissues. HAE is associated with high morbidity and mortality, because patients have disabling angioedema attacks, usually inadvertently undergo exploratory laparotomy as a result of abdominal angioedema, and live with the risk of having laryngeal angioedema that can lead to death due to asphyxia. Therefore, proper management of these patients is essential to improve their quality of life and minimize the risks.¹

Pharmacotherapy of HAE is divided into 3 modalities: long-term prophylaxis, short-term prophylaxis, and treatment of acute attacks. The objective of long-term prophylaxis in HAE is to reduce the frequency and severity of attacks, and it should be personalized based on 4 variables: frequency and severity of HAE attacks, impact of these attacks on the patient's quality of life, and availability of treatment for HAE attacks. Worldwide, 3 treatment modalities for long-term prophylaxis have been used: attenuated

androgens, antifibrinolytic agents, and plasma-derived C1 inhibitor (pdC1-INH). The first 2 have been available for a long time, have lower cost, and do not require intravenous access for administration. However, there are concerns about their side effects, which can be prevented by pdC1-INH replacement. During pregnancy, for long-term prophylaxis of HAE with C1-INH deficiency, pdC1-INH is the drug of choice, whereas antifibrinolytic agents have been used with extreme care and attenuated androgens are contraindicated.²

There are very few scientific data regarding long-term prophylaxis of HAE with normal C1-INH, especially during pregnancy. Estrogens are relevant triggering factors involved in female patients with HAE, and symptoms may become more frequent and severe during pregnancy. Estrogens increase FXII mRNA transcription and stimulate release of Hsp90, activating the prekallikrein-high-molecular-weight kininogen (HK) complex to generate kallikrein and bradykinin.^{3,4} We reported 3 pregnant women with HAE with normal C1-INH who were successfully treated in long-term prophylaxis with pdC1-INH. These patients had normal functional and quantitative C1-INH levels. Our study suggests that a therapeutic dose of pdC1-INH leading to a supra-physiological serum concentration of this protein could inhibit bradykinin production, which is increased in these patients.⁵ We acknowledge and congratulate Gibbons et al,⁶ who contemporaneously with us reported a case similar to our 3 cases, although they denominated their patient's long-term prophylaxis as "perinatal" or "near-term" prophylaxis.⁷

After the advances observed in the treatment of HAE acute attacks, we will soon face a revolution in the disease long-term prophylaxis, including with the availability of new drugs such as subcutaneous C1-INH concentrate, lanadelumab, and BCX7353 (an oral small-molecule inhibitor of plasma kallikrein). The studies performed by us and Gibbons et al brought scientific evidence that supports the use of pdC1-INH in long-term prophylaxis of HAE with normal C1-INH.^{5,7} Further studies may corroborate this new indication of pdC1-INH in the long-term prophylaxis of HAE with normal C1-INH.

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