



Letter

Successful prophylaxis with recombinant human C1 inhibitor in a patient with hereditary angioedema

Hereditary angioedema (HAE) caused by C1 inhibitor (C1-INH) deficiency is a rare, autosomal-dominant, life-threatening disorder. The lack of C1-INH results in the activation of the complement, coagulation, kinin, and fibrinolytic systems, which leads to the generation of bradykinin. This vasoactive mediator increases vascular permeability and causes the development of recurrent angioedema in subcutaneous and/or submucosal tissues (eg, in the gastrointestinal wall or the upper airway mucosa).¹

Although the onset of the edematous episodes is unpredictable, many episodes occur during specific life circumstances or events.² According to empirical observations, physical exertion, mechanical trauma, mental stress, infection, menstruation, pregnancy, medical interventions, changes of the weather, and treatment with certain medicinal products are associated with an increased risk of a HAE attack.

Most of the literature on preprocedural treatment reports the prevention of edematous episodes associated with surgical or diagnostic interventions (dental procedures, primarily) performed on the head and the neck.³ The role of medical procedures in the pathophysiology of edema formation is unclear. The tissue injury that results from surgical trauma involves the release of phospholipid molecules from the damaged cells, leading to the activation of the Hageman factor, which could trigger the kinin-kallikrein plasma cascade system.⁴

The international therapeutic guidelines on HAE caused by C1-INH recommend introducing short-term prophylaxis before medical interventions.^{5,6} This treatment modality may significantly reduce the occurrence of edematous episodes. High-dose attenuated androgens, antifibrinolytic agents, fresh frozen plasma, and plasma-derived C1-INH concentrate are suitable prophylactic agents. Regarding preprocedural prophylaxis, however, only plasma-derived C1-INH concentrates have gained regulatory approval and only in Europe. The new innovative medicines (the kallikrein inhibitor ecallantide, the bradykinin β_2 -receptor antagonist icatibant, and the recombinant human C1-INH) have been licensed for short-term treatment only.^{5,6}

The following is the first report, to our knowledge, on the prophylactic efficacy of recombinant C1-INH administered for preprocedural prophylaxis in the clinical setting.

The 51-year-old woman with type 1 HAE caused by C1-INH had been experiencing HAE symptoms since the age of 3 years. Her condition was diagnosed 2 decades later, at 23 years of age. Her father and one of her brothers died of laryngeal edema at the age of

38 and 27 years, respectively. Her other 3 siblings and her daughter also have HAE caused by C1-INH.

After the diagnosis, the frequent recurrence of severe edema required prophylactic, long-term pharmacotherapy with danazol, 200 mg/d. Acute episodes were relieved by the administration of fresh frozen plasma. After her third pregnancy (at the age of 27 years), the patient underwent a series of dental procedures. During a 2-year period, she had 4 dental extractions always followed by edema of the face, lips, and eyelids, which resolved spontaneously in 3 to 4 days. She had dental filling on 6 occasions, including 4 performed while she was under local anesthesia with lidocaine. The latter 4 interventions were followed by facial edema, which receded without intervention in 3 days. Edema did not occur after the remaining 2 dental fillings performed without anesthesia.

The patient was referred to our angioedema center at the age of 37 years. She was taking danazol for long-term prophylaxis; we recommended plasma-derived C1-INH to relieve acute edematous episodes. The patient has been followed up at annual visits. After 12 years, she requested replacing plasma-derived C1-INH concentrate with recombinant human C1-INH on religious grounds. After 1½ years of on-demand recombinant therapy, she has experienced 63 acute episodes, which were always responsive to acute recombinant human C1-INH administration.

This March, filling the right lower second incisor was necessary while she was under local anesthesia with lidocaine. The patient received one vial (2,100 IU) of recombinant human C1-INH 1 hour before the intervention, and another vial of the drug was kept available during the procedure. The dose of danazol was the same before and after the intervention, which was uneventful (edema did not develop).

Highly purified, recombinant human C1-INH (Ruconest; Pharming Technologies BV, Leiden, The Netherlands) is produced and purified from the milk of pathogen-free transgenic rabbits. Theoretically, it is less suited for prophylaxis because its half-life is shorter than that of plasma-derived C1-INH (3 vs 36–48 hours).⁷ Notwithstanding this, clinical relapses were not observed in any of the recent studies. Choi et al⁸ hypothesized that transient restoration of C1-INH levels is sufficient to block the various activated pathways that are involved in the pathogenesis of an angioedema attack. Moreover, weekly administrations of 50 IU/kg of recombinant human C1INH appeared to reduce the frequency of HAE attacks and were generally safe and well tolerated.⁹ These observations and our case support that recombinant human C1-INH might prove suitable also for short-term prophylaxis in HAE caused by C1-INH; however, multicenter studies are needed to enhance the efficacy and safety of this agents.

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