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Clinical trial supports use of novel preventive therapy for dangerous swelling disorder

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clinical trial for a new drug to prevent attacks of hereditary angioedema (HAE) - a rare disorder characterized by recurrent swelling of tissues in the face, hands, gastrointestinal tract and airway - has had promising results. In the February 23 *New England Journal of Medicine*, a multi-institutional team describes how subcutaneous injection of the monoclonal antibody lanadelumab every 14 days significantly reduced swelling episodes without serious side effects in HAE patients.

"In this study we found that lanadelumab appears to be safe and well tolerated in HAE patients, and early data in a small number of patients suggests strong efficacy," says Aleena Banerji, MD, of the Massachusetts General Hospital (MGH) Division of Rheumatology, Allergy and Immunology, corresponding and a lead author of the NEJM publication. "A larger phase 3 study to evaluate the efficacy of lanadelumab is now underway."

HAE is caused by mutations that reduce the production or expression of the C1 inhibitor protein - an enzyme that inhibits the activity of proteins involved with inflammatory, blood coagulation and other systems. Without the action of the C1 inhibitor protein, the kallikrein-kinin cascade is not inhibited, leading to excess generation of bradykinin, which causes vascular leakage and is responsible for the swelling seen in HAE patients.

The uncontrolled swelling resulting from HAE attacks not only restricts the activities of patients, sometimes for several days, but also can be life-

threatening when the airway is involved. While on-demand treatment administered during an attack is essential, preventing attacks would be beneficial for many patients. However, the currently FDA-approved preventive therapies have limitations. Attenuated androgens can have significant side effects and are not safe during pregnancy, and intravenous C1 inhibitor is often inconvenient and needs to be administered every three or four days.

The NEJM publication reports on a double-blinded, phase 1b clinical trial of lanadelumab, a monoclonal antibody that inhibits the action of kallikrein, potentially blocking the cascade leading to bradykinin generation. The study enrolled 37 patients with HAE resulting from C1 inhibitor deficiency, who were divided into five groups. Four groups received two subcutaneous injections of lanadelumab 14 days apart - for total dosages of 30 mg, 100 mg, 300 mg or 400 mg - the other group received injections of a placebo. Participants were followed for 120 days after the second injection.

The occurrence of adverse events related to treatment - primarily pain at the injection site and headache - was similar across all groups, and no serious events were reported, supporting the safety of the treatment. In participants receiving doses totaling 300 mg or 400 mg, the action of kallikrein was found to be inhibited in a dose-dependent manner. In participants who had an average of two or more HAE attacks in the three months prior to enrollment, efficacy was evaluated in the 300 mg and 400 mg groups. In the period from day 8 to day 50 after the initial injection, none of the five participants receiving 300 mg and only two of the eleven receiving 400 mg had an attack. In contrast, eight of the eleven patients in the placebo group had HAE attacks during that period.

"If this kind of efficacy is seen in the larger phase 3 trial, which is now underway here at MGH and many other sites, this could significantly improve the quality of life for patients with HAE," says Banerji, who is

an associate professor of Medicine at Harvard Medical School. The co-lead author of the NEJM paper is Paula Busse, MD, of Icahn School of Medicine at Mt. Sinai in New York. The study was supported by Dyax, the developer of lanadelumab, which is now part of Shire.

More information: Aleena Banerji et al, Inhibiting Plasma Kallikrein for Hereditary Angioedema Prophylaxis, *New England Journal of Medicine* (2017). DOI: 10.1056/NEJMoa1605767