New drug shown safe, effective in treating hereditary angioedema

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Clinical trials from two international research teams have shown that icatibant, a new drug that blocks the action of an inflammatory protein known as bradykinin, is safe and effective in treating acute attacks of hereditary angioedema, a potentially life-threatening condition. In their report in the August 5 *New England Journal of Medicine*, the authors note that - while the results of one trial did not reach statistical significance - the drug is safe and effective and further study will help clarify the patients and symptoms best treated with icatibant.

"We have not had many options for treating painful, debilitating and potentially life-threatenting attacks of hereditary angioedema, and these studies showed that icatibant improves symptoms and is not associated with any concerning side effects," explains Aleena Banerji, MD, of the Massachusetts General Hospital (MGH) Rheumatology, Allergy and Immunology Division, corresponding and co-lead author of the NEJM paper, who also was principal investigator of the MGH study site.

Hereditary angioedema (HAE) is caused by low levels or poor function of a protein called C1 esterase inhibitor. Patients with the condition suffer recurrent episodes of swelling caused by fluid leaking from blood vessels. The swelling can involve the face, extremities, gastrointestinal tract and the throat or larynx, where it can cause potentially life-threatening airway blockage. HAE is believed to affect at least one in 50,000 people, and treatment has been focused on preventing attacks and relieving symptoms. The FDA has approved C1 esterase inhibitor infusions for treatment of HAE, and an injected drug that inhibits the

enzyme kallikrein also recently recieved approval to treat acute HAE attacks. But that approval stipulated the treatment could only be administered by a health care professional because of the risk of anaphylactic reactions.

Icatibant blocks the receptor for bradykinin, a protein that dilates and increases the permeability of blood vessels and produces many symptoms of inflammation. Bradykinin is believed to mediate many symptom of HAE, so a drug that interferes with its action was felt to be a good candidate to treat HAE attacks. Manufactured by the German pharmaceutical firm Jerini, Inc., icatibant has received approval in the European Union, where it is marketed under the brand name Firazyr. The NEJM study reports on two phase 3 trials - one based in the U.S. the other in Europe - conducted as part of the Jerini's application to the U.S. Food and Drug Administration.

Both studies were randomized, double-blind, prospective trials enrolling adults who had been diagnosed with HAE. The U.S.-based trial, called FAST-1, compared icatibant with a placebo for treatment of acute attacks; while the European trial, FAST-2, used trenaxminic acid, an oral medication available in Europe, as the comparison drug. Study participants - 56 for FAST-1 and 74 for FAST-2 - returned to their enrollment site for treatment within six hours of onset of a moderate to severe HAE attack. Response to the study medication was assessed by both patients themselves and by study investigators, who primarily evaluated the time required for relief of the most severe symptom and secondarily evaluated relief of all symptoms.

In both studies, icatibant produced faster symptom relief than the comparison drug, but the difference was much greater in the FAST-2 trial that used trenaxminic acid for comparison. The authors note that the less significant results seen in FAST-1 may reflect aspects of the study design - particularly the fact that success was determined based on relief

of the most serious symptom only. The limited size of the study groups means that they may have differed in the primary symptoms patients experienced. In addition, more FAST-1 participants received C1 esterase inhibitor injections as rescue treatment, which may have hidden the extent of icatibant-associated symptom improvement. No serious treatment-related adverse events were reported in either trial.

"These data do show that HAE patients receiving icatibant improve, and the drug seems to be very safe," says Banerji. "A larger, worldwide phase 3 trial of icatibant is currently in process and should help us clarify the picture further." Banerji is an assistant professor of Medicine at Harvard Medical School.

Provided by Massachusetts General Hospital

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