Proof-of principle study finds imatinib improves symptoms for patients with severe asthma

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Mast cells, a type of white blood cell, are present in the airways of severe asthmatics even in the face of aggressive treatment, and their presence is associated with key indicators of severe asthma. It has long been thought that these mast cells contribute to the disease and that targeting them may improve symptoms and quality of life for patients with severe asthma. In a new, proof-of-principle study published in the *New England Journal of Medicine*, researchers from Brigham and Women's Hospital have found that targeting the mast cells with imatinib, a drug used to effectively treat certain forms of cancer, improved airway hyperresponsiveness, a measure of the sensitivity of the airway, and decreased the number of mast cells present in the airway. Treatment also produced a small improvement in airway function.

"By targeting these mast cells, we can actually make a difference for our patients with severe asthma," said Elliot Israel, MD, a physician and researcher in the Division of Pulmonary and Critical Care Medicine at BWH and senior author of the paper. "This is an exciting development because patients with severe asthma often have poor disease control even when adhering to our best and most aggressive therapies."

Imatinib (brand name Gleevec), is one of the first precision medicine cancer therapies and is currently used to effectively treat certain forms of cancer that have a specific mutation. It works by targeting the processes responsible for mast cell development, stem cell factor and its receptor, the KIT receptor tyrosine kinase, which are essential for not only normal mast cell development but also their survival. These new results suggest that KIT-dependent processes and mast cells contribute to the process of severe asthma, and suggest that imatinib and drugs that can inhibit mast cell development may be effective therapies for patients with severe asthma who do not respond well to current treatment options.

"This study shows how the investigator community begins to apply knowledge of basic disease pathogenesis to tailor interventions to specific patient populations, which leads to more effective therapy. This is particularly the case for this patient group with a disease that is difficult to treat and that has a high morbidity rate," said James Kiley, Ph.D., director, Division of Lung Diseases, at the National Heart, Lung, and Blood Institute (NHLBI).

In a double-blind, placebo-controlled 24-week trial of 62 participants with poorly-controlled severe asthma, researchers evaluated the impact of imatinib on the change in airway hyperresponsiveness and mast cell presence. Participants in the treatment group received imatinib for six months. Participants underwent a bronchoscopy with airway biopsy at the beginning and the conclusion of the study to assess airway mast cells. Airway responsiveness and airway function were also measured during the study.

Israel and his colleagues report that patients in the treatment group experienced a reduction in airway hyperresponsiveness compared to placebo. Specifically, after three months, airway responsiveness decreased 50 percent in those treated with imatinib compared to those who received placebo. A similar degree of difference was seen between the groups at six months. Additionally, researchers found that imatinib reduced serum tryptase, a marker of mast cell activation, compared with placebo. Researchers also report that patients in the treatment group experienced a relaxation and opening up of the airways, which was an unexpected observation. Researchers note that patients in the treatment

group experienced higher rates of muscle cramps and an abnormally low level of phosphate in the blood.

While the results are preliminary, Israel and colleagues found that imatinib was more effective in patients who had less eosinophils, a type of disease-fighting white blood cell present in high numbers in certain types of severe asthma.

"There are several new drugs for severe asthma that target the more allergic, or eosinophilic, type of severe asthma. If confirmed, our finding - that targeting mast cells is effective for patients who do not have eosinophilic-type asthma - is particularly exciting because this group of patients, which make up about 40 percent of patients with severe asthma, have no current treatment options to control their disease."

Researchers note that larger-scale studies are needed to confirm their finding and evaluate longer durations of therapy in order to definitively determine clinical efficacy. Planning for these trials is underway.

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