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Novel Drug Offers Hope for Early Intervention in Cystic Fibrosis Patients

Cystic Fibrosis (CF) patients with normal to mildly impaired lung function may benefit from a new investigational drug designed to help prevent formation of the sticky mucus that is a hallmark of the disease, according to researchers involved in a phase 3 clinical trial of the drug. Called denufosol, the investigational medication can be given early in the CF disease process, and may help delay the progression of lung disease in these patients, the researchers found.

The findings were published online ahead of the print edition of the American Thoracic Society's American Journal of Respiratory and Critical Care Medicine.

"Although the lungs of children with CF are thought to be normal at birth, studies have demonstrated significant lung damage that occurs early in life in children suffering from cystic fibrosis," said lead investigator Frank Accurso, MD, Professor of Pediatrics, University of Colorado School of Medicine, Denver. "Many patients continue to suffer progressive loss of lung function despite treatment of complications. Because denufosol can be used early in life, it offers hope for delaying or preventing the progressive changes that lead to irreversible airflow obstruction in CF patients."

Denufosol belongs to a class of drugs known as ion channel regulators. These drugs help balance the flow of ions through cell membranes, helping normalize the airway surface hydration and mucus clearance impairment present in patients who suffer from the disease. In cystic fibrosis, the ion sodium chloride does not flow normally through cell membranes, resulting in thick, sticky mucus which is difficult to cough out of the airways. In addition to causing breathing problems, the mucus becomes a breeding ground for bacteria and can cause serious respiratory infections.

Denufosol works by increasing chloride secretion, inhibiting sodium absorption and increasing the beat frequency of the tiny hairs, or "cilia," lining the airways move to clear mucus. Combined, these effects enhance airway hydration and aid in clearing mucus. The drug is different from other CF medications, which primarily treat the symptoms rather than the underlying causes, said Dr. Accurso, who is also the director of University of Colorado's cystic fibrosis center.

This study is the first large, phase 3 trial of an ion channel regulator in cystic fibrosis patients with little or no baseline pulmonary function impairment.

"Abnormal ion transport and defective mucociliary clearance are fundamental defects that contribute to complications of CF lung disease, including mucus plugging, chronic bacterial infection, inflammation and progressive airway damage," Dr. Accurso noted. "Although currently available drugs target these complications, denufosol was designed to treat the underlying defects that cause the complications, and could potentially modify the course of the disease, particularly when administered early in the disease process."

Researchers enrolled 352 cystic fibrosis patients 5 years of age or older, and enrolled them to receive either inhaled denufosol or placebo three times daily for 24 weeks, followed by a 24-week open-label period when all patients received denufosol. At baseline, most patients enrolled had mild impairment of lung function and were taking multiple medications to control their symptoms. Because the study outcomes were measured using spirometry, a lung function test that can be difficult to accurately use in young children, patients under five years of age were excluded.

Patients' exhalation rates and lung volume were measured throughout the study, and also were monitored for adverse events, such as cough, congestion, fever or sinusitis. At the end of the 24-week period, researchers determined

patients who received denufosol had better lung exhalation rates than those in the placebo group, whose exhalation volumes remained relatively unchanged from the start of the study. Both groups had similar numbers and types of adverse events, with the denufosol patients experiencing significantly fewer headaches and lower rates of sinusitis and runny nose.

Although children under five years of age were excluded from this study, Dr. Accurso said future studies likely would address the use of denufosol in this younger population.

"Considering the evidence that early inflammation and infection results in impaired lung function and structural damage in early childhood, future studies of the effects of denufosol during the first 5 years of life is warranted," he said.

A second, similar phase 3 trial incorporating a longer placebo-controlled treatment phase is ongoing to further investigate the effectiveness of denufosol in patients with CF, Dr. Accurso added.

Frank J Accurso, Richard B Moss, Robert W Wilmott, Ran D Anbar, Amy E Schaberg, Todd A Durham, Bonnie W Ramsey, and the TIGER-1 Investigator Study Group. Denufosol Tetrasodium in Patients with Cystic Fibrosis and Normal to Mildly Impaired Lung Function. American Journal of Respiratory and Critical Care Medicine, 2010; DOI: 10.1164/rccm.201008-1267OC