Commonly used 3-drug regimen for idiopathic pulmonary fibrosis found harmful

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The National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health, has stopped one arm of a three arm multi-center, clinical trial studying treatments for the lung-scarring disease idiopathic pulmonary fibrosis (IPF) for safety concerns. The trial found that people with IPF receiving a currently used triple-drug therapy consisting of prednisone, azathioprine, and N-acetylcysteine (NAC) had worse outcomes than those who received placebos, or inactive substances.

"These findings underscore why treatments must be evaluated in a rigorous manner," said Susan B. Shurin, M.D., acting director of the NHLBI. "This combination therapy is widely used in patients with IPF, but has not previously been studied in direct comparison to a placebo for all three drugs."

The interim results from this study showed that compared to placebo, those assigned to triple therapy had greater mortality (11 percent versus 1 percent), more hospitalizations (29 percent versus 8 percent), and more serious adverse events (31 percent versus 9 percent) and also had no difference in lung function test changes. Participants randomly assigned to the triple- therapy arm also remained on their assigned treatment at a much lower rate (78 percent adherence versus 98 percent adherence).

"Anyone on some combination of these medications with questions or concerns should consult with their health care provider and not simply stop taking the drugs," said Ganesh Raghu, M.D., professor of medicine

at the University of Washington, Seattle and a co-chair of this IPF study. "It is important to realize that these results definitively apply only to patients with well-defined IPF and not to people taking a combination of these drugs for other lung diseases or conditions."

The other two study arms, or intervention groups, of this IPF trial comparing NAC alone to placebo alone will continue. In stopping this part of the trial, the NHLBI accepted the recommendation of the Data and Safety Monitoring Board (DSMB) – an independent advisory group of experts in lung disease, biostatistics, medical ethics, and clinical trial design. The DSMB has been monitoring the study since it began.

This study, called PANTHER-IPF (Prednisone, Azathioprine, and N-acetylcysteine: A Study that Evaluates Response in Idiopathic Pulmonary Fibrosis) was designed and conducted by the Idiopathic Pulmonary Fibrosis Clinical Research Network, funded by the NHLBI. The PANTHER-IPF study was designed to evaluate whether this commonly used triple-therapy regimen could slow disease progression and improve lung function in people with moderate IPF.

PANTHER-IPF was the first study in IPF comparing the effectiveness of this combined treatment to a placebo for all three drugs. Each participant had a one in three chance of being randomized to receive the triple drug regimen, NAC alone, or placebo for a period of up to 60 weeks.

"We will continue to analyze the data to try to understand why this particular combination may be detrimental in people with IPF," said Fernando Martinez, M.D., professor of medicine, University of Michigan, Ann Arbor and co-chair of the PANTHER-IPF study. "The results are not explained by any differences between the two groups before the treatments started."

IPF is a progressive and currently incurable disease characterized by the buildup of fibrous scar tissue within the lungs. This accumulation of scar tissue leads to breathing difficulties, coughing, chest pain, and fatigue. Approximately 200,000 people in the United States have IPF. The cause or causes of IPF remain unknown; as a result treatment options remain limited. PANTHER-IPF began enrollment in October 2009.

The study had enrolled 238 of a planned 390 participants prior to the stop announcement. Participants ranged from 48 to 85 years of age, with an average age of 68. The placebo and NAC arms will continue enrolling and following their participants, and this part of the PANTHER-IPF study is expected to be completed by late 2013.

More information: What is Idiopathic pulmonary fibrosis? www.nhlbi.nih.gov/health/health-topics/topics/ipf/

Find more information about this clinical trial at clinicaltrials.gov/ct2/show/NCT00650091

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