IPF drug fails in new trial

EurekAlert

A new study has demonstrated no significant benefit of taking the drug bosentan for idiopathic pulmonary fibrosis (IPF).

The results were published online ahead of the print edition in the American Thoracic Society's *American Journal of Respiratory and Critical Care Medicine*. Read the full study here [1].

Although the primary endpoint of the Bosentan Use in Interstitial Lung Disease (BUILD)-3 study was not attained, researchers point to the possibility of benefit for a subset of IPF patients who had undergone surgical lung biopsy to confirm their diagnosis. The study, however, had insufficient power to confirm this finding.

"The effects of the drug were not great enough to detect with statistical significance in the population that we examined," said lead author of the study, Talmadge King, Jr., chair of the Department of Medicine at the University of California, San Francisco. "While these results are certainly not what we had wanted, we did find reasons to hope that we may yet demonstrate that bosentan does a have a beneficial effect in a select group of IPF sufferers."

Three years ago, Dr. King and colleagues conducted the BUILD-1 trial, a prospective, double-blind, placebo-controlled trial designed to determine whether bosentan could improve six-minute walk distances in IPF patients after one year. That trial failed to demonstrate a difference in six-minute walk distances, but a post-hoc analysis suggested that patients who underwent surgical lung biopsy to confirm their IPF diagnosis had improvements in their health-related quality of life and delayed worsening of their IPF.

The BUILD-3 trial was designed to refine the patient population that appeared to benefit from bosentan in BUILD-1 and assess the effects of the drug more precisely. The randomized, double-blind placebo-controlled study enrolled a total of more than 600 patients were enrolled and randomized 2:1 to receive bosentan or a placebo. Patients were eligible if they had mild to moderate IPF, confirmed by surgical lung biopsy, for three years or less. Patients with extensive honeycombing (indicating more advanced disease) were excluded.

Each patient was assessed at baseline, at randomization, and every four months thereafter until the conclusion on the study. The primary endpoint of the study was IPF worsening or all-cause death. IPF worsening was defined as a decrease of at least 10 percent in forced vital capacity and at least 15 percent in the DLCO, confirmed by tests four weeks apart.

Secondary endpoints included changes in health-related quality of life, time to IPF worsening and time to death.

The patients were followed for a mean of 19.9 months until the end of the study, which was predetermined to be when 202 IPF-related "events"?that is, worsening or death?occurred. There was no significant difference between treatment and placebo groups for time to death or to IPF worsening.

"This outcome was very disappointing," said Dr. King. "We have long believed that treatment of patients with early disease would stack the deck in favor of any potentially effective therapy for IPF. That did not happen in this study."

Health-related quality of life scores were also not significantly different between groups. There was a small, non-significant delay to time of IPF worsening up to End of Study (excluding death) between patients receiving bosentan and those on placebo. There was also non-significant evidence of a positive effect of bosentan on loss of lung function as measured by FVC and DLCO.

"This study was rigorously designed to elucidate the effect suggested by BUILD-1," said Dr. King. "Unfortunately, despite the rigorous and clinically important endpoints, we were unable to demonstrate the expected results. However, there is hope that endothelin antagonists, alone or in combinations with other anti-fibrotic agents, can benefit a certain subpopulation of people with IPF; our goal moving forward to is to identify that population more precisely."

"Although this was a negative study, these investigators continue to move us toward finding effective treatments for IPF, primarily because they have advanced our understanding of how to design rigorous clinical trials for IPF, which has been extremely difficult to study," said John E. Heffner, MD, past president of the American Thoracic Society. "As these investigative approaches are applied to other potential drug therapies, we anticipate it is only a matter of time until we discover ways to improve the course of patients with IPF."

SOURCE [2]

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