Statins may increase risk of interstitial lung abnormalities in smokers

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Use of statins may influence susceptibility to or the progression of interstitial lung disease (ILD) in smokers, according to a new study.

While some studies have suggested that statins might be beneficial in the treatment of fibrotic lung disease, others have suggested that they may contribute to the progression of pulmonary fibrosis by enhancing secretion of inflammasome-regulated cytokines, and numerous case reports have suggested that statins may contribute to the development of various types of ILD.

"Based on earlier case reports of statin-associated ILD and data suggesting that smoking is associated with the interstitial lung abnormalities (ILA) which underlie ILD, we hypothesized that statins would increase the risk for ILA in a population of smokers," said George R. Washko MD, MMsC, and Gary M. Hunninghake MD, MPH, of the Division of Pulmonary and Critical Care at Brigham and Women's Hospital in Boston. "Accordingly, we evaluated the association between statin use and ILA in a large cohort of current and former smokers from the COPDGene study. In addition to the association between statin use and ILA we found in humans, we also demonstrated that statin administration aggravated lung injury and fibrosis in bleomycin-treated mice." Bleomycin has been shown to induce lung inflammation and fibrosis.

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

Assessment included pulmonary function testing and CT scanning for radiologic features of ILA. Among 1,184 subjects with no evidence of ILA, 315 (27%) used statins, compared with 66 of 172 (38%) subjects with ILA. After adjustment for a number of covariates, including a history of high cholesterol or coronary artery disease, statin users had a 60 percent increase in the odds of having ILA , compared to subjects not taking statins. No other positive associations between ILA and cardiovascular medications or disorders were detected. The association between statin use and ILA was greatest with statins with higher hydrophilicity (readily absorbed or dissolved in water), such as pravastatin, and in higher age groups.

The effects of statins on lung injury and fibrogenesis were also examined in a study in mice, which were pretreated with pravastatin prior to intratracheal bleomycin administration. Statin use was found to exacerbate bleomycin-induced lung fibrosis. In a further in vitro study, statin pretreatment was shown to enhance Nlrp3-inflammasome activation through mitochondrial reactive oxygen species generation in macrophages. "These results implicate activation of the NLRP3 inflammasome in fibrotic lung disease," said Jin-Fu Xu MD, and Augustine M. K. Choi, MD, of the Department of Pulmonary Medicine, Shanghai Pulmonary Hospital, Tongji University School of Medicine, in Shanghai, China and the Division of Pulmonary and Critical Care at Brigham and Women's Hospital in Boston, respectively.

There were some limitations to both studies. Findings in the mouse model were not replicated in human samples. All study subjects were current or former smokers, perhaps limiting the applicability of the results to others. Cigarette smoking by itself may lead to pulmonary inflammation. Finally, the duration and dosage of statin therapy was not available for the majority of patients.

"While statin use was associated with ILA in our study, caution should be used when extrapolating these findings to the care of patients," concluded Dr. Hunninghake. "The significant benefits of statin therapy in patients with cardiovascular disease probably outweigh the risk of developing ILA, and

statin use may benefit some patients with respiratory disease. Clinicians should be aware, though, that radiological evidence of ILD can develop in some patients treated with statins."

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