New therapy found for rare lung disorder

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Researchers at the University of Cincinnati (UC) and Cincinnati Children's Hospital Medical Center have found that the FDA-approved drug sirolimus, used primarily to prevent rejection in organ transplant patients, stabilized lung function in women with lymphangioleiomyomatosis (LAM).

The Multicenter International LAM Efficacy of Sirolimus (MILES) trial was the first randomized, controlled study designed to develop a therapy for this life-threatening illness, which currently has no cure or treatment.

These results are being reported in the March 16, 2011, online edition of the *New England Journal of Medicine*.

LAM is a progressive, cystic lung disease that occurs almost exclusively in women. In LAM, an unusual type of smooth muscle cell grows uncontrollably and spreads from an unknown source to restricted areas in the body, including the lungs, lymph nodes and vessels and kidneys, limiting the flow of air, blood and lymph.

Shortness of breath and recurrent lung collapse are common in patients with LAM, and until now, lung transplantation has been the only hope for patients who progress to respiratory failure.

"LAM affects about five people per million and occurs in 30 to 40 percent of women with tuberous sclerosis complex (TSC), a genetic disorder which also causes tumors to form in the kidneys, brain, heart and other organs," says Frank McCormack, MD, director of the

pulmonary, critical care and sleep medicine division at UC and lead investigator on the study.

"Sirolimus, otherwise known as rapamycin, showed promise for patients with LAM in a pilot study conducted in Cincinnati and reported in the New England Journal of Medicine in 2008, but the relative risks and benefits of sirolimus for treatment of patients with this condition have remained unclear. In this international, multicenter study, we evaluated the safety and efficacy of one year of sirolimus in stabilizing and/or improving lung function in women with LAM."

McCormack says LAM cells isolated from lung lesions have TSC mutations and exhibit activation of a key sirolimus-sensitive growth pathway. When exposed to the drug in culture, the growth of LAM cells is stopped.

Experiments in TSC animal models have also demonstrated that sirolimus shrinks tumors in the liver and kidneys.

The MILES study was conducted within the National Institutes of Health (NIH)-supported Rare Lung Diseases Consortium, led by UC and Cincinnati Children's physician and pulmonary biologist Bruce Trapnell, MD, and co-directed by McCormack, and involved 13 institutions from around the world. Data was reported using Internet-based systems connected to a centralized, Internet-based data coordinating center headed by Jeffrey Krischer, MD, at the University of South Florida, Tampa.

"The trial included a screening visit and a year-long double blind, placebo-controlled treatment period, followed by a year of observation," says McCormack.

All eligible participants were female, aged 18 years or older and had a

confirmed diagnosis of LAM with abnormal lung function.

Patients meeting the criteria were randomly assigned to either receive an initial dose of oral sirolimus at 2 milligrams per day or a matched placebo, and sirolimus levels were measured at each follow-up visit. Results were revealed only to an independent medical monitor who made dosing recommendations to maintain serum levels within a pre-specified target range.

A total of 89 patients with LAM were enrolled in the United States, Canada and Japan. Patients underwent baseline lung function testing, and lung function and exercise outcomes were measured over the course of six visits in the first year. Participants were also given questionnaires to determine how their symptoms changed throughout the course of the study.

Researchers found that sirolimus stabilized lung function and was associated with improvement in measures of functional performance and quality of life.

Sirolimus also reduced levels of serum vascular endothelial growth factor-D, or VEGF-D, a protein that is known to be elevated in LAM. VEGF-D promotes the growth of lymphatic vessels and can be involved in the spread of cancers.

"After discontinuation of sirolimus, lung function decline resumed and paralleled the placebo group," McCormack says. "Adverse events were more common with sirolimus, but the frequency of serious adverse events between the groups was not different."

McCormack says that these results suggest that sirolimus may be useful as therapy for moderately severe LAM-related lung disease.

"LAM is typically slowly progressive, and sirolimus therapy has risks, so treatment decisions should be individualized. Care must be taken in generalizing the results to those with milder or more severe lung disease due to LAM," he says. "Also, additional trials are needed to determine the optimal dose and duration of treatment with sirolimus. Given the toxicity profile of the drug during a one-year period, the long-term safety of this approach over an extended course must be carefully evaluated."

The trial involved efforts by the LAM Foundation that lobbied for the NIH's attention, organized and recruited patients and supported pivotal basic and clinical research that formed the scientific basis for the study.

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