Transplant drug sirolimus shrinks tumors, improves lung function

9 January 2008

The drug sirolimus, normally used to help transplant patients fight organ rejection, may eventually be used as a less invasive treatment for a tumor called angiomyolipomata in patients with who would otherwise face surgery. The finding is reported by investigators from Cincinnati Children's Hospital Medical Center and the University of Cincinnati College of Medicine in the Jan.10 edition of *The New England Journal of Medicine*.

One year of treatment with sirolimus significantly reduced the size of angiomyolipomata by nearly 50 percent in patients with tuberous sclerosis complex (TSC), a rare genetic multi-system disease, or lymphangioleiomyomatosis (LAM), a rare cystic lung disease, according to results of the phase I/II proof-of-concept trial. Sirolimus also improved lung function in the LAM patients. Both TSC and LAM are associated with gene mutations that result in inappropriate activation of mTOR (mammalian target of rapamycin), an enzyme that helps control the growth and proliferation of all cells. Sirolimus inhibits mTOR signaling, researchers said.

"Less invasive therapies are clearly needed to treat the angiomyolipomata that people with TSC and LAM develop, and a drug that maintains or shrinks tumor size may reduce the need for procedures such as surgery," said John Bissler, M.D., lead author of the study and a physician/scientist in the Division of Nephrology and Hypertension at Cincinnati Children's. "Our data suggest that mTOR inhibition with sirolimus may hold promise for treating these and other disease manifestations in patients with TSC and LAM."

In the study, tumor volume in 20 patients treated with sirolimus for 12 months had significant reductions of about 50 percent. In 18 patients evaluated 12 months after sirolimus treatment stopped average tumor volume had increased again to about 85 percent of the original size.

Five of the 18 patients evaluated 12 months post treatment had a persistent tumor volume reduction of 30 percent or more. Bissler and his coauthors speculate that regression in angiomyolipoma size might stem from a form of programmed cell death called apoptosis or cell-volume reduction.

In 11 study participants with LAM, 12 months of sirolimus treat resulted in a 10 to 15 percent improvement in expiratory air flow, a standard measurement of lung function. One year after sirolimus treatment ended, the treatment effect waned somewhat, but remained substantially above the level of lung function that would have been expected over two years with no treatment. Researchers said improved pulmonary function was likely caused by a reduction of gas trapping in the lungs and a decrease in airflow obstruction. Lung function for people with LAM often declines to the point that patients require oxygen and eventually a lung transplant.

Sirolimus treatment led to several side effects, including mouth ulcers, diarrhea, upper respiratory infections and joint pain.

Researchers also noted limitations in the study's open-label design, lack of a control group and small number of study participants. However, given the effects of sirolimus in the trial the researchers at Cincinnati Children's are optimistic about its potential.

Support for the phase I/II proof-of-concept study came from the patient advocacy groups, the LAM Foundation and the Tuberous Sclerosis Alliance (made possible in part by a grant from the Kettering Fund), Wyeth, the National Cancer Institute and National Institutes of Health.

Dr. Bissler and his colleagues are pursuing additional trials to further define the relative risks and benefits of mTOR inhibitors in patients with LAM and TSC. Dr. Bissler is leading another trial to see if different dosing of mTOR inhibitors improves

the effectiveness of treating angiomyolipomata tumors, and is working to launch a placebo-controlled multinational trial to better understand the effects of this therapy on angiomyolipomata.

Frank McCormack, M.D., a physician and researcher at the UC College of Medicine, is leading multi-institutional Phase III trial of sirolimus involving 120 patients with LAM that is randomized, double-blind and placebo-controlled. David Franz, M.D., a physician and researcher at Cincinnati Children's, is conducting a trial to see if mTOR-inhibitor therapy helps the specific TSC-related brain lesion subependymal giant cell astrocytoma, and is working on a second placebo-controlled, multinational trial for this treatment.

Source: Cincinnati Children's Hospital Medical Center