MedicalXpress

New genes at work in patients with hereditary lung disease

August 10 2009

University of Florida researchers have safely given new, functional genes to patients with a hereditary defect that can lead to fatal lung and liver diseases, according to clinical trial findings slated to appear this week in the online early edition of the *Proceedings of the National Academy of Sciences*.

Three patients, apparently for the first time in their lives, were able to produce trace amounts of the protective form of a protein called alpha-1 antitrypsin for up to one year, a potential step toward a gene therapy for about 100,000 Americans with alpha-1 antitrypsin deficiency.

In the study, researchers with UF and the University of Massachusetts describe how they injected into patients' upper arms doses of a harmless virus containing copies of the correct gene for alpha-1 protein.

In most people, alpha-1 antitrypsin is made in the liver and protects the lungs by fighting inflammation.

Without it, people are vulnerable to infections or irritants in the air, such as cigarette smoke, and often develop life-threatening lung disease.

"When you give this therapy into the deltoid muscles of the arm, the muscle becomes a factory for making the protein that these individuals are missing," said Dr. Mark L. Brantly, a professor of medicine and molecular genetics and microbiology at UF's College of Medicine and first author of the study. "The amounts produced were not at therapeutic

levels, but the fact we were able to get any produced is an important concept — the proof of principle that it can be done."

The trial established the safety of the adeno-associated virus used to "infect" patients' cells with replacement genes, which then do the vital work of producing alpha-1 protein. Furthermore, researchers were able to detect alpha-1 antitrypsin in patients' plasma a year after treatment, showing that the normal gene was successfully transferred and doing its intended job in the patients' muscles.

"What I would tell the alpha-1 community is that this trial does not give us any guarantee, but there is a fighting chance to develop a therapy using this method," said senior author Dr. Terence Flotte formerly the chairman of pediatrics at UF and now the dean of the School of Medicine, and provost and executive deputy chancellor of UMass Medical School. "In every patient at the highest dose in this study, we saw transgene expression. And although it approached just 1 percent of what we ultimately want, we can be reasonably optimistic that we can achieve much closer to normal values in people by using the same approach with an increased dose."

Nine alpha-1 patients were divided into three groups to receive the gene therapy at the General Clinical Research Center at Shands at UF medical center. Patients received nine injections in their non-dominant upper arms, with the dosage increasing in each group. At 365 days after the injections, the transferred genes were measurably producing alpha-1 protein in the three patients who received the highest dose.

Although patients showed some elevated immune response to the gene therapy vector — which is designed to break down quickly after delivering its cargo — researchers did not detect any evidence that the patients' bodies rejected the transferred genes or the newly created protein.

"That's a really good sign," said Brantly, a member of the Powell Gene Therapy Center and the UF Genetics Institute, who sees about 150 alpha-1 patients in his medical practice. "After we gave the injections, the individuals stayed on the ward for five days while we monitored them. There were no ill effects, only a minimal amount of redness, and by the end of the five days most of the subjects were bored."

Some people with alpha-1 deficiency lead disease-free lives, never knowing they have defective genes. In others, the deficiency can lead to emphysema and cirrhosis, both progressive diseases that can be fatal.

Currently, the only limitedly effective treatment for patients with serious breathing symptoms involves weekly intravenous injections of alpha-1 protein derived from human plasma. The injections must continue throughout a patient's life, according to the American Lung Association. It does not cure the disease, but it does appear to slow the progression.

"This study gives us encouraging evidence that gene therapy for Alpha-1 is a realistic possibility," said John Walsh, president and chief executive officer of the nonprofit Alpha-1 Foundation, which has been supporting research of this kind for more than a decade. "The augmentation therapy available now has slowed down the progression of our lung disease and extended many of our lives. The promise of gene therapy addresses our ongoing issues of convenience, such as weekly infusions, and affordability. The hope of gene therapy is that we may have a one-time, brief series of injections that could allow our own bodies to produce the alpha-1 protein we need to live a normal lifetime.

"The Alpha-1 community is incredibly grateful for the progress that these dedicated investigators have made," Walsh said.

Source: University of Florida (news : web)