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Promising gene therapy for Duchenne muscular dystrophy

‘Most exciting treatment’ in history of muscular dystrophy, says UC Davis Health expert

(SACRAMENTO)

Clinical researchers at UC Davis Health are using a gene therapy approach for Duchenne muscular dystrophy (DMD), the rare genetic disease that mainly occurs in boys and causes a steady loss of muscle and premature death.

Renowned DMD expert Craig McDonald is helping lead a promising clinical trial for Duchenne muscular dystrophy (pre-COVID photo).

The physician overseeing the clinical trial at UC Davis Medical Center in Sacramento calls the experimental therapy “the most exciting treatment” he’s seen in the history of muscular dystrophy.

“This is really transformational treatment for children with muscular dystrophy,” said Craig McDonald, professor and chair of the Department of Physical Medicine and Rehabilitation and a renowned expert on Duchenne. “Children with Duchenne lack the dystrophin protein, which is an essential protein for muscle strength and development. This gene therapy product leads to production of a shortened form of the dystrophin that addresses the underlying cause of DMD. This micro-dystrophin has the potential to halt the disease progression and could lead to physiological improvement for patients.”

The clinical trial, which includes UC Davis Medical Center and several other sites, involves a single infusion of an experimental gene therapy.

Duchenne is caused by a genetic mutation that prevents the body from producing fully functional dystrophin, a large cytolinker protein that connects the interior of the cell to the extracellular matrix.

Dystrophin is expressed in many tissues of the body, but it has the critical role of stabilizing the muscle membrane (sarcolemma) when muscles contract.

Without dystrophin, Duchenne patients' muscle cells become damaged and weaken. Muscle weakness becomes increasingly noticeable between the ages of 3 and 5. By the time most patients are 12 years old, they often require a wheelchair. During adolescence, heart and breathing muscles weaken, leading to serious, life-threatening complications.

McDonald has been working for nearly three decades with Duchenne patients. For this investigation, he and his team are using an adeno-associated *virus* (*AAV)* vector – AAVrh74 – as the gene transfer platform. However, there is a limitation on the size of the gene that can be carried in an AAV viral vector. The solution: miniaturize the gene to fit it into the AAV transmission vector. The unique *micro-dystrophin* gene contains the important functional aspects of the gene. Those include production of the normal binding domains of the protein, as well as the critical elements needed to restore muscle function.

If the experimental gene therapy is successful, it is hoped to significantly restore motor function in patients. McDonald likes to envision that someday DMD patients treated early with gene therapy will be able to run, jump and hop like other children.

"Most of the treatments that have targeted dystrophin restoration historically have achieved levels that are relatively lower compared to this transformational treatment," McDonald added. "This gene therapy produces levels of the replacement micro-dystrophin protein that are closer to normal levels."

The gene therapy may also help reduce the leading cause of death in Duchenne patients: heart and respiratory diseases. Because the treatment targets both skeletal muscle and cardiac muscle, it could benefit cardiac and pulmonary functions in patients.

The multi-center trial UC Davis is participating in will involve over 20 Duchenne patients, and the hope is that eventually this therapy could be beneficial to a wide range of patients with Duchenne, including teenage patients who can no longer walk. The researchers will be studying the how the quantity of patients' micro-dystrophin protein expression changes over 12 weeks. Patients will be followed for five years after dosing.

McDonald noted that this is an open-label trial using a commercially available cellular therapy product. Both participants and their families, as well as the researchers, are aware of the product that is being tested. He hopes that with a demonstrated increase in micro-dystrophin levels, data from this research could help accelerate the FDA approval process. The ultimate goal is enabling the treatments to reach a wider range of children with Duchenne muscular dystrophy.