MedicalXpress

Clinical trial first to test heart drug regimen for Duchenne muscular dystrophy

June 26 2012

The first landmark randomized clinical trial for a cardiac drug regimen in Duchenne muscular dystrophy (DMD) is testing whether earlier treatment can stop or slow down heart damage that usually kills people with the disease.

The study is a collaboration of Cincinnati Children's Hospital Medical Center, Ohio State University (OSU) and The Christ Hospital in Cincinnati.

Extensive research – including studies in mouse models of DMD – suggests an anti-fibrosis drug long used to treat heart attack victims, eplerenone, could help people with the disease, said Kan Hor, MD, a principal investigator and a physician/researcher at Cincinnati Children's.

Disease-associated heart damage is the leading cause of death in patients between ages 20 and 30 – the maximum life span for people with DMD.

A key element of the new treatment approach is using enhanced cardiac magnetic resonance imaging, Hor said. The technique – more sensitive than standard echocardiogram tests now used in DMD – is designed to catch minute declines in heart function much earlier in a child's life.

"Standard diagnostic techniques rarely catch significant heart damage in DMD in the first decade, although research shows scar tissue is already developing in many patients before it's clinically detectable through

current methods," said Hor, who works in the Cincinnati Children's Heart Institute. "We want to determine the optimal time point to detect these early changes in heart function and start cardiac therapy with anti-fibrotic medication."

A genetic disease that affects mostly boys, DMD is the most common form of muscular dystrophy. Most children begin losing the ability to walk between the ages of 7 and 13. With decades of research, testing and increased emphasis on multidisciplinary care, physicians have been able to use steroids and other drugs to preserve some ambulation, pulmonary function and push survival ages well into the 20s.

Still, there remains no consensus on how to best manage DMD-associated heart fibrosis and disease, Hor said. Often, between the ages of 7 and 10, echocardiogram results

show the heart is functioning normally by conventional measures – delaying needed heart treatment in an intensely time-sensitive disease.

Evidence-driven approach

Hor and his colleagues theorize earlier diagnosis and treatment with anti-fibrotic medication could enhance quality of life and survival for people with DMD. They base this on a broad range of studies at Cincinnati Children's and other institutions, including reviews of clinical data.

One stark conclusion from those reviews is that, by the time current diagnostic methods catch DMD-associated heart disease after the age of 10, damage is often irreversible. By then, standard treatment with beta-blockers and angiotensin converting enzyme inhibitors provide little if any long-term benefit.

One study co-authored by Hor reviewed the cases of 247 children with

DMD. Thirteen percent of patients under the age of10 years already had significant evidence of cardiac scarring – even though conventional tests indicated normal heart function.

Standard echocardiograms now used in DMD look for declines in left ventricle ejection fraction (LVEF) – a measure of heart muscle pumping ability. Although reliable for many heart conditions, functional assessments by echocardiograms are not sensitive enough to detect early DMD-associated heart disease, such as heart muscle fibrosis, scarring and important functional decline that precedes measurable LVEF reductions.

To overcome this limitation, the clinical trial is using advanced cardiac magnetic resonance imaging (CMR) techniques. They include imaging with a contrast agent called gadolinium, which allows physicians to detect the early formation of heart muscle fibrosis while patients are still young and ejection fraction is normal.

The image analysis includes an overlay tool that divides the heart into 24 equal sub-segments. As the heart beats, the segment grids move in line with the region of the heart they cover. The grids start out as perfectly square, but then contort in conjunction with a twisting motion the heart makes to force blood through the body. This allows physicians to measure heart function region by region to catch the smallest of declines.

"On an individual basis, measuring each of the grids doesn't tell you very much," Hor explained. "But when you add up the grids, you can see cumulative changes and catch small but important declines in heart function. We believe this test will help us pick the best time to begin drug treatment."

Preclinical drug tests

The decision to test the drug eplerenone is based in part on extensive clinical studies of DMD patients at Cincinnati Children's and in mouse models of DMD at OSU spear led by Dr. Hor's collaborator Dr. Subha Raman. Another factor is its success in treating people with certain types of advanced heart disease.

The drug is an aldosterone antagonist, a diuretic that helps the body get rid of excess fluid (tissue swelling) while retaining sufficient potassium levels. It blocks the buildup of fibrotic material and scarring that over time can turn heart muscle into non-functioning fatty tissue.

The drug's success in treating fibrosis in adult heart patients has led to it being sought for off-label treatment in patients with DMD, creating a sense of urgency behind the current clinical trial, Hor said.

In the mouse studies, early treatment with eplerenone resulted in reduced heart fibrosis and improved cardiac function. Researchers treated two groups of mice, one at 8 weeks of age and a second at 4 weeks. As the mice aged, the researchers noted normal LVEF and functional improvement in both groups, although reported the benefit was more pronounced in mice treated earlier at 4 weeks.

"The results of that research indicated that earlier treatment with this medication offers an excellent chance of preserving heart function, decreasing fibrosis and reducing cardiac death in DMD," said Hor.

The Phase 2/3 double-blind randomized clinical trial will treat 40 patients initially for one year, focusing on patients older than 7 years of age with evidence of heart muscle scarring but normal heart function as determined by LVEF.

The study is supported in part by Ballou Skies, Parent Project Muscular Dystrophy (PPMD), and The Lindner Center for Research & Education

at The Christ Hospital Foundation. Long time research collaborator, Dr. Wojciech Mazur from The Christ Hospital in Cincinnati, is also assisting with the trial.

Hor said treatment with eplerenone will be compared to a placebo and current standard drug treatments. Depending on trial results, the research could move into a larger trial to include more patients at different stages of heart disease. Hor said he expects the current trial to take about 12-18 months to enroll patients and a little over two years to complete.

More information: Additional information is available at: clinicaltrials.gov/ct2/show/NC … ne&recr=Open&rank=15

Provided by Cincinnati Children's Hospital Medical Center