Global Study Focuses on Novel Treatment for Rare Form of Heart Failure

All cases of heart failure aren't created equal, but University of Maryland Medical Center (UMMC) is taking part in an international clinical trial to determine if an investigational drug can slow the progression of one of the most uncommon types of this increasingly common and deadly condition.

UMMC is one of 50 sites worldwide — with others in North America as well as in South America, Europe and Japan — testing the effectiveness of the oral medication tafamidis for transthyretin cardiomyopathy, also known as TTR-CM. A little-known, progressive and fatal condition affecting an unknown percentage of the nation's 5.1 million heart failure patients, TTR-CM is triggered when transthyretin, a transport protein normally circulating in the blood as a quatramer, "misfolds" and builds up in the heart muscle as amyloid fibrils. The fibrils cause the heart muscle to stiffen which leads to heart failure.

Stephen S. Gottlieb, M.D., a professor of medicine at University of Maryland School of Medicine and UMMC's lead investigator in the study — the first phase 3 trial of its type for cardiac symptoms of TTR mutations — has done decades of research in heart failure involving both the pathophysiology and treatment of the condition. But this research is enticingly different, he says, helping to bring fresh attention to an under-recognized origin of heart failure and potentially provide a therapy attacking this cause.

"Realizing that amyloidosis is a significant and underappreciated contributor to heart failure, it was pretty straightforward that I'd want to be involved in figuring out the characteristics of this disease and what we can do to treat it," he explains. "We have thought that TTR-CM is like a needle in a haystack, but it's probably not true — I think we've just been missing it."

TWO TYPES ADD UP TO ONE MAJOR PROBLEM

With an estimated life expectancy of three to seven years after a diagnosis of TTR-CM, pinpointing the disease early is critical. Two types exist: TTR familial amyloid cardiomyopathy, which is the hereditary form of the condition; and so-called "wild type" or senile TTR cardiomyopathy, which doesn't have a genetic basis. Both types, however, result in the same symptoms that plague many heart failure patients, including shortness of breath and swelling in the extremities.

While much is still unknown about TTR-CM, several facts have become apparent. The inherited version of the disease appears to affect 3% to 4% of African-Americans of both genders — typically striking in their 50s or 60s — and up to 10% of African-Americans with heart failure have the TTR-CM mutation. The non-genetic or wild type version, on the other hand, seems to disproportionately affect Caucasian men over 65.

"In the United States, probably more common is the hereditary amyloidosis that occurs in African-Americans, although other genetic variations also lead to the disease. In addition, although we don't know the underlying cause, amyloidosis can develop in older people," says Dr. Gottlieb. "Very often, physicians will think that somebody who has heart failure has a thickened heart because of hypertension, and they don't realize it may be amyloidosis."

Aside from using established at-risk patient populations as clues to whose heart failure may stem from TTR-CM, doctors can zero in on EKG results that exhibit inappropriately low voltage (even if criteria for low voltage are not met in patients who appear to have hypertrophic hearts), Dr. Gottlieb says. The condition also can be reliably diagnosed by MRI

KEY POINTS:

- UMMC is one of 50 sites worldwide testing novel drug for rare cause of heart failure called transthyretin cardiomyopathy, or TTR-CM
- TTR-CM affects 3% to 4% of African-Americans through genetic mutation
- Caucasian males over age 65 disproportionately affected by non-genetic version of condition
- Phase 3 clinical trial testing oral medication tafamidis against placebo for TTR-CM treatment
- 300 participants will be followed for 30 months for outcomes

MEMBERS OF THE RESEARCH TEAM INCLUDE: (FROM L TO R) Jennifer Marshall, BS; Dana Beach, BSN; Shawn Robinson, MD; Stephen Gottlieb, MD; and Joanne Marshall, BSN MS.

abnormalities. Additionally, genetic testing can reveal carriers of the mutated TTR gene — which can also manifest as neuropathy and disorders of other organ systems — and a myocardial biopsy can definitively diagnose the TTR cardiomyopathy.

"Once suspected, there are many ways to find it," he says. "We think it's common and not recognized enough. But there are many clinically important implications, since traditional heart failure treatment doesn't do much to address the problems of TTR-CM patients. Furthermore, some treatments can make their heart failure worse and are dangerous with amyloidosis."

INVESTIGATIONAL DRUG FILLS VOID

The drug at the center of the clinical trial, tafamidis, has already been approved in Europe for neurological symptoms triggered by TTR mutations. It is believed to work by hindering amyloid formation and deposits by stabilizing the transthyretin quatramer. Side effects are considered minor, including gastrointestinal upset.

The double-blind, placebo-controlled study, initiated about a year ago, will include about 300 total participants, giving approximately 180 patients the oral daily medication and 120 patients the placebo. Over 30 months, patients will be followed for outcome measures ranging from six-minute walking test scores and TTR stabilization to cardiovascular-related hospitalizations and death.

If proven to slow progression of patients' heart failure, tafamidis would fill a decidedly large void in treatment options for the condition, Dr. Gottlieb says. UMMC has treated certain advanced TTR-CM patients carrying the genetic mutation with heart-liver transplants, since the TTR protein is produced primarily in the liver.

HIGH HOPES FOR FUTURE USE

"There's a non-steroidal that's been used for amyloidosis of other organs," he notes, "but in heart failure, renal function becomes very important, so non-steroidals are contraindicated. Until now, there really has not been a real medical treatment for TTR amyloidosis."

Even if the clinical trial produces strong results supporting tafamidis' effectiveness, it may take five more years to obtain FDA approval. In the meantime, Dr. Gottlieb is hoping that the study leads to improved identification of patients with TTR cardiomyopathy and longer survival and better quality of life.

"We all believe that identification of genetic causes of heart failure can lead to more effective individualized care, and detection of people genetically at risk for TTR cardiomyopathy is a prime way to prove this hypothesis," he says. "Right now we're trying to help people who have symptoms, but we hope we can do even more in the future. Assuming this drug works, perhaps many cases of heart failure can be prevented." ✚

For further information, please call **420-328-8790** or email Dr. Gottlieb at **sgottlie@medicine.umaryland.edu**.