New drug offers hope for patients with rare genetic heart disease

More patients being recruited here for trial of treatment based on gene-editing tech

Zhaki Abdullah
Correspondent

A new drug based on gene-editing technology could soon provide respite to patients suffering from a rare and potentially fatal genetic heart disease.

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a rare disease of the heart muscle that involves deformed transthyretin (TTR) proteins building up in the heart, nerves and other organs.

As a result of the protein build-up, the walls of the heart become thickened and stiff. The heart cannot then relax properly and get filled with blood, and it cannot pump it efficiently to the rest of the body.

The symptoms of ATTR-CM can be vague and may include numbness in the hands and feet, lethargy and dizziness; but left undiagnosed and not treated promptly, it could lead to heart failure and death.

The disease affects about 150 people in Singapore, but Assistant Professor Lin Weiqin – clinical director for the heart failure and cardiomyopathy programme at the National University Heart Centre, Singapore (NUHCS) – believes the number could be much higher.

This is because those affected often dismiss the symptoms – including swelling in the legs, numbness in the hands and unsteady walking – as normal consequences of ageing, Prof Lin said, noting that such symptoms can also be attributed to other conditions.

"Not many patients know about this condition, and not many doctors can diagnose this condition accurately as well," he said, noting that NUHCS first set up a registry for ATTR-CM patients in 2019.

Nexiguran Ziclumeran, a new drug that is also known as nex-z or NTLA-2001, seeks out and removes a portion of the TTR gene, slowing down the production of the disease-causing protein.

It is based on Crispr-Cas9 technology, the Nobel Prize-winning gene-editing tool which has been used to alter DNA sequences.

US biotechnology firm Intellia Therapeutics, which developed nex-z, is now conducting a worldwide trial involving 765 patients with ATTR-CM and a history of heart failure to evaluate its efficacy.

Recruitment for the double-blind trial – where neither the participants nor the researchers know who received the actual treatment and who received a placebo – in Singapore began in 2024.

Eight patients have already been recruited from NUHCS and the National Heart Centre Singapore, and Prof Lin, who is leading the study here, said they hope to recruit a total of 14 patients by end-2025.

Prof Lin noted gene editing therapy has already been approved in other countries for treating certain neuromuscular conditions, cancers and inherited blood disorders.

"If this trial is successful, it will be the first DNA-altering treatment used in the field of adult cardiology and offers new hope to patients living with ATTR-CM," he said.

Patients in Singapore who wish to take part in the trial must be aged between 18 and 90, and diagnosed with heart failure due to ATTR.

They must also be on medication for heart failure and have experienced heart failure in the past year.

As a precaution, only women who can no longer have children are eligible to participate in the trial, as the edited genes could be passed down, said Prof Lin.

One of those recruited is Mr Chua Ah Hai, who began experiencing numbness and weakness in his hands following a car accident in 2018.

Doctors originally diagnosed Mr Chua, who was working as a baker then, with carpal tunnel syndrome – a common condition among those who work with their hands.

An abnormal heart scan, however, suggested a deeper problem, and a heart biopsy confirmed that the father of two had ATTR-CM.

"I couldn't carry heavy things after my condition deteriorated. I stopped work in March 2024, as my employers encouraged me to rest," said the 61-year-old, noting he often fell down and sustained fractures as a result of his condition.

He took part in the trial as he believed it could benefit his condition.

"I wanted to give myself a new hope, a new lease of life," he said.

Mr Chua's son and daughter, aged 27 and 26, were tested and found to be positive for the gene mutation that causes the disease, though they have shown no symptoms and have been asked to monitor their conditions.

A parent with the gene mutation that causes familial ATTR-CM has a 50 per cent chance of passing it to each of his or her children, according to the Cleveland Clinic; but not every child who inherits this gene mutation develops ATTR-CM.

Though the outcomes of the study will only be known in about two to three years, early phase clinical trials – whose findings were published in the New England Journal Of Medicine in November 2024 – showed "consistent, rapid, and durable reductions" in the abnormal protein that causes ATTR-CM, with minimal side effects.

Patients enrolled in the trial here have also not reported any side effects, Prof Lin noted.

Another trial will begin to study the effectiveness of nex-z on patients with transthyretin amyloid neuropathy, where the accumulation of TTR proteins results in nerve damage.

The National University Hospital (NUH) and the Singapore General Hospital are recruiting patients for this, with Dr Kay Ng – a senior consultant at NUH's neurology division – leading recruitment for NUH.

Should the trials prove successful, those who initially received a placebo will also receive a free dose of nex-z, said Prof Lin, adding that he expects the drug to become commercially available by the end of the decade.

azhaki@sph.com.sg

Mr Chua Ah Hai (seated), who has transthyretin amyloid cardiomyopathy, with (from left) Prof Lin Weiqin, clinical director for the heart failure and cardiomyopathy programme at the National University Heart Centre, Singapore (NUHCS), Dr Kay Ng, senior consultant at NUH's neurology division, and clinical research coordinator at NUHCS Nur Faezah Md Fadzillah. ST PHOTO: AZMI ATHNI