Novel gene-editing therapy shows promise for patients with transthyretin amyloid cardiomyopathy

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A single IV infusion of NTLA-2001, a novel CRISPR/Cas9-based gene editing therapy, significantly reduced circulating transthyretin (TTR) protein levels in patients with ATTR amyloid cardiomyopathy, a

progressive and fatal cause of heart failure, according to late-breaking research presented today at the American Heart Association's Scientific Sessions 2022. The meeting, held in person in Chicago and virtually, Nov. 5–7, 2022, is a premier global exchange of the latest scientific advancements, research and evidence-based clinical practice updates in cardiovascular science.

Transthyretin is a protein that is produced by the liver and transports retinol, also known as vitamin A, and the thyroid hormone thyroxine in circulation through the body. Transthyretin amyloidosis (ATTR) is caused by accumulation of fibrils composed of misfolded transthyretin protein in organs including the heart. The fibrils disrupt normal organ function and lead to progressive organ failure.

"Despite the availability of TTR protein stabilizers as a treatment option for people with ATTR amyloidosis, it remains a progressive and universally fatal disease," said lead study author Julian D. Gillmore, M.D., Ph.D., a professor at the University College London Center for Amyloidosis in the U.K. "Recently, clinical trials investigating therapy with gene-silencing agents targeting mRNA have found that lowering TTR protein levels results in cardiac benefits."

Researchers evaluated the safety, tolerability and efficacy of NTLA-2001, which precisely knocks out the TTR gene in the liver of people with ATTR amyloid cardiomyopathy. A single IV dose of NTLA-2001 is designed to minimize production of the abnormal TTR proteins.

The study included 12 participants with ATTR amyloidosis and varying levels of heart failure requiring treatment. Patients received a single infusion of NTLA-2001. Levels of TTR protein concentration in the bloodstream were measured at the beginning of the study and also at periodic intervals—two, four and six months—after the single

intravenous NTLA-2001 dose.

The results found that circulating serum TTR proteins were rapidly and profoundly reduced by at least 90% in all patients 28 days after administration of a single intravenous dose of NTLA-2001. These benefits were sustained through to the last study visit conducted between four and six months after receiving the therapeutic infusion. In addition, NTLA-2001 was generally well-tolerated (meaning that there was only one serious adverse event, which resolved), and the majority of adverse events, such as infusion-related reactions, were mild.

The primary limitation to interpretation of this study is that it is an original, Phase 1 dose escalation study in patients with ATTR amyloid cardiomyopathy, Gillmore said.

"This is the first-ever human trial of gene editing in vivo, or in the body, and our study proves that gene editing in the human body is possible and also safe in the short term. We were impressed by the significant and consistent reductions in patients' serum TTR protein levels," Gillmore said.

"These results indicate that IV NTLA-2001 is a potential new treatment option that may stop disease progression in patients with ATTR amyloid cardiomyopathy or even bring about improvement. However, further research is needed to establish long-term safety of NTLA-2001 and to continue to monitor and evaluate the potential effects of markedly reduced TTR levels on patients' clinical outcomes."

More information: Link to session abstract

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