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Intellia says CRISPR treatment safely corrects DNA of six patients with rare disease

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By Megan Molteni[2] [3]Sept. 16, 2022

Ruby Wallau for STAT

Intellia Therapeutics said Friday the first six patients to receive its CRISPR-based treatment for a genetic swelling disorder have safely had small, corrective changes made to dysfunctional DNA inside their liver cells.

Preliminary results from the study — just the second to show that

CRISPR-based gene editing can be delivered systemically and performed in vivo, or inside the body — found that the treatment, NTLA-2002, reduced levels of the disease-causing protein, kallikrein, by 65% and 92% in the low- and high-dose cohort, respectively. In the low-dose group, the one-time infusion also reduced by 91% the painful swelling "attacks" commonly experienced by patients with a rare condition called hereditary angioedema, or HAE. Participants in the high-dose group have not yet completed the 16-week observation period.

"These initial data represent a significant milestone for both Intellia and people around the world suffering from genetic diseases, such as HAE," said Intellia CEO John Leonard, in a statement.

The data were presented Friday at the Bradykinin Symposium in Berlin, Germany.

A debilitating disease that can sometimes be fatal, hereditary angioedema is caused by a defect in a gene that controls production of a blood protein called C1 inhibitor — leading to excess amounts of two other related proteins. This oversupply causes blood vessels to discharge a deluge of fluid into the body, resulting in painful "attacks" of swelling. Often, these attacks involve the hands, feet, and face, but swelling can also occur in the intestinal wall — causing abdominal pain, nausea, and vomiting — or in the airways, where it can be deadly.

Worldwide, about 200,000 people are estimated to be living with hereditary angioedema, including fewer than 8,000 individuals in

the U.S. Earlier this month, Intellia announced that the U.S. Food and Drug Administration has granted orphan drug status to NTLA-2002, which will allow the drug maker seven years of marketing exclusivity upon FDA approval.

Today, HAE patients rely on injectable medicines to curb the pain and swelling brought on by recurrent attacks. Takhzyro, marketed by Takeda, is the leading preventative treatment on the market and it also works by suppressing the same cascade of protein malfunctions. But it requires twice-monthly injections to be most effective.

In the pivotal clinical trial that supported Takhzyro's approval, an every-two-week injection schedule led to an 87% reduction in the rate of HAE attacks, relative to placebo. When injected just once monthly, the drug cut HAE attack rates by 73%.

To be competitive, NTLA-2002 needed to show similar reductions in the HAE attack rate — at least by 90%, according to analysts and investors.

Approximately 60% of patients with HAE in the U.S. regularly take Takhzyro or other drugs that aim to prevent or reduce the frequency of swelling attacks. Intellia's approach offers those patients the possibility of a one-and-done infusion, which would remove the burden of lifelong treatment. But with only a few months of follow-up data so far, it's too early to say if NTLA-2002 can deliver on that promise.

But what NTLA-2002 is starting to show is the promise of a

platform technology like lipid nanoparticle-delivered CRISPR[6] to address any genetic disease where there is a liver-expressed protein.

Last summer, Intellia became the first of the so-called CRISPR companies[7] to present clinical data showing it's possible[8] to precisely alter the DNA of particular cells within the body with a one-time intravenous infusion of CRISPR components. Other companies developing treatments based on CRISPR either perform the work on cells in a lab[9] and then re-administer them to patients, or inject them directly[10] into the target tissue.

Intellia's lead candidate, NTLA-2001, being co-developed with Regeneron for treating transthyretin amyloidosis, targets the progressive disease by sending CRISPR to faulty versions of patients' TTR gene residing in their liver cells. Once there, it makes cuts to the gene, disabling it and preventing those cells from pumping out misshapen, mangled proteins that then accumulate in other tissues and cause problems.

In February, the companies reported[13] that in patients with a form of the disease that impacts the peripheral nervous system, their CRISPR-based therapy reduced the levels of mutated versions of the protein transthyretin by 93% — a decrease that was sustained for at least nine months.

On Friday, Intellia announced that in patients in the cardiomyopathy arm of the study — who have a different form of transthyretin amyloidosis that causes the toxic protein to

accumulate mostly in heart tissue — NTLA-2001 knocked down levels of transthyretin by 92%-94% across three doses infused into 12 participants.

The updated study results remain preliminary, but provide further evidence that a one-time intravenous infusion of NTLA-2001 can effectively shuttle CRISPR to the target cell population inside the body, and once there, make the desired edits to the DNA of those cells.

But there's still a lot to prove through clinical trials, including whether the edits in the liver translate into meaningful improvement in disease-related cardiac symptoms.

Data on suppression of the toxic TTR protein from trials of two approved drugs — Alnylam Pharma's Onpattro and Ionis Pharmaceuticals' Tegsedi — have shown that the higher the reduction in protein concentrations, the better the outcomes for patients with hereditary transthyretin amyloidosis. But there's a much larger group of patients who have a version of the disease where the TTR protein isn't mutated and misshapen.

In this so-called wild-type disease, the protein is normal but still accumulates in the hearts and tendons of elderly people. The cardiomyopathy arm of Intellia's NTLA-2001 trial includes patients with both the mutated and wild-type versions of the problematic protein.

"For wild-type, we don't have any data yet that says what percent knockdown will lead to clinical improvement," said Rodney Falk,

a cardiologist and director of the Cardiac Amyloidosis Program at Brigham and Women's Hospital. Falk was not involved in the NTLA-2001 study but reviewed the data at STAT's request. "This is great science, but we've got a long way to go before getting excited."

Adam Feuerstein contributed reporting.

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