MedicalXpress

Stanford patient is first infant to receive lifesaving drug for neurodegenerative disease

December 6 2016

In 2013, Zoe Harting became the first baby in the world to receive an experimental drug that her doctors hoped would save the lives of thousands of infants like her.

Zoe has spinal muscular atrophy type 1, a degenerative neuromuscular disease that kills most patients by their second birthday.

Before she began receiving the drug, 7-month-old Zoe was quite weak. She couldn't sit up or roll over. She couldn't move her legs at all, or lift her arms when she was lying down. She struggled to swallow. Her parents, John and Eliza Harting, knew that without an effective treatment, she would soon struggle to breathe. But no treatment had ever succeeded against SMA-1. So when the Hartings got a call from Stanford pediatric neurologist John Day, MD, PhD, asking if they would consider enrolling Zoe in a phase-2 clinical trial of an experimental drug called nusinersen, they agreed.

"I've seen so many kids die with this disease," said Day, who directs the Neuromuscular Disorders Clinic at Lucile Packard Children's Hospital Stanford and is a professor of neurology and of pediatrics at the Stanford University School of Medicine.

SMA-1 is the most common genetic cause of death in infants. It's triggered by a gene mutation that is carried by 1 in 40 people. The disease, which occurs when a child inherits the mutated gene from both parents, is diagnosed in about 250 babies per year nationwide. In the

past, pediatric neurologists could help make patients comfortable as their health declined, but that was all. "We would have to tell the parents, 'I'm sorry, we don't have anything that will stop the progression of the disease,'" Day said.

The drug nusinersen is changing that.

Improvement in meeting motor milestones

On Dec. 6, the results of the phase-2 trial that Zoe Harting helped to launch will be published in *The Lancet*. Day is a co-author of the study, which was led by pediatric neurologist Richard Finkel, MD, of Nemours Children's Hospital in Orlando, Florida. Nusinersen is safe and well-tolerated, the study reports. Although the multisite trial included only 20 children and was intended primarily as a safety test, the investigators report significant improvements in patients' ability to achieve motor milestones, as well as better motor function and increased function of nerves that are attacked by the disease.

The drug is quickly progressing through the regulatory approval process. In addition to the phase-2 trial in which Zoe participated, nusinersen has been evaluated in a phase-3 trial of SMA-1 patients, which was stopped early in August because it was obvious that infants receiving the drug were achieving significantly more motor milestones than those in the control group. The phase-3 trial is now an open-label study, meaning that all participants can receive nusinersen.

The drug is expected to receive approval from the FDA within the next two months, and in the interim is available under an expanded access program at a few sites around the country, including Lucile Packard Children's Hospital Stanford.

"This drug really, really, completely turns things around for SMA," Day

said. "It's huge." An even larger discovery is that drugs with the same mechanism of action may help treat other genetic diseases, he added. Nusinersen is an antisense oligonucleotide, which works by sticking to a specific piece of genetic material. Trials of antisense oligonucleotide drugs are now underway for other neurological diseases, including muscular dystrophy, Huntington's disease and amyotrophic lateral sclerosis.

A painful diagnosis

When Zoe was born, in October 2012, the El Granada, California, infant seemed healthy. But after several weeks, John and Eliza suspected she might be weakening, and a Christmas visit with Eliza's extended family solidified their worries. Zoe was moving much less than her baby cousin, who was a week younger.

"It was really noticeable that they were very different," John Harting said. "Her cousin was rolling over and Zoe was almost immobile."

Their pediatrician referred Zoe to a neurologist, who diagnosed SMA-1.

"It was really, really hard," John said. "That neurologist basically told us she would not live past 2, and that we could only hold her, love her and let her die."

The Hartings are both involved in scientific research: John is a bioinformatician, and Eliza a statistician. They began searching for clinical trials Zoe could join, and found a new pediatrician who connected them to Day. Though the nusinersen trial had not yet enrolled any patients, doctors at four sites in the United States and Canada were looking for infants with recently diagnosed SMA-1 who might be good candidates. The drug had already been given to older children with a milder form of spinal muscular atrophy to test its safety, but physicians

needed to try it in babies with SMA-1 to discern if it caused a measurable improvement in symptoms. Day asked the Hartings to let Zoe be the first.

John Harting read some of the scientific papers explaining how nusinersen was expected to function. "What I read suggested it was a good bet, and the only one available at the time," he said. "We decided we had to take this chance."

What goes wrong in SMA-1

SMA-1 develops in babies who inherit two faulty copies of the SMN1 gene, which encodes a protein called survival motor neuron. The protein maintains nerves that carry signals from the spinal cord to muscles; without it, these nerves degenerate. Muscles atrophy to the point that, eventually, the patients can't move, swallow or breathe.

However, most people have a second gene called SMN2, which is 99 percent identical to the SMN1 gene but makes very little functional protein.

"SMN2 doesn't work well," Day said. "It's like you've got a spare tire, but it's flat."

Nusinersen can, in effect, inflate the spare tire. Compared to SMN1, there is a difference of just one base pair in the genetic code of SMN2 that greatly reduces its production of full-length messenger RNA, the molecule needed to carry genetic information from DNA to the cells' protein-making machinery. Nusinersen binds to the faulty mRNA, allowing it to be constructed correctly and increasing the production of functional SMN protein.

Day and his colleagues hoped nusinersen would provide SMA-1 patients

with enough survival motor neuron protein to reduce the impact of the disease.

"It was anxiety-producing for all of us at the outset," Day said. "What kept me awake at night was that I wondered if we were going to create this bad situation where we might keep Zoe's diaphragm working but she would otherwise be devastated." Day told the Hartings he worried Zoe might improve just enough to stay alive, but that her quality of life would be poor. "We talked about it, and they were willing to give it a try and see what happened," he said.

Gaining strength

In June 2013, Zoe began receiving doses of nusinersen. To reach the nerves where it is needed, the drug is injected into the spinal fluid once every few months.

The next year was difficult. Because SMA-1 had hurt Zoe's nerves so much before the drug trial began, her breathing and coughing were weak. Several colds landed her in the intensive care unit with pneumonia, and whenever she seemed to grow stronger, another bout of illness weakened her again.

Finally, near Zoe's second birthday, everyone was convinced that she was gaining strength. Remarkably for a toddler with SMA-1, she could lie on her back, lift her legs and play with her toes.

"She started picking up milestones and doing things that were totally unexpected," Day said. "It was incredible."

Soon afterward, Zoe started speaking. Her ability to cough improved, helping her fight off respiratory germs. She gained control over her head, then got strong enough to sit if someone helped her up into a

seated position.

Today, 4-year-old Zoe is still making gradual improvements. She can eat, talk, yell and tussle with her little sister. She has learned to scoot around in a motorized wheelchair. She goes to preschool. She likes to play catch with her dad. Her parents recently bought her a recumbent bicycle, which they hope will help strengthen her legs, a step that once seemed far too much to hope for.

"She continues to slowly gain motor skills; it's quite unexpected and rewarding," said Day.

"It's a world of difference," added John Harting.

The outlook for SMA-1 patients who receive nusinersen soon after their diagnosis is even better than for patients like Zoe, who was already weak when she began getting the drug, Day said.

"If we identify children early on, before they become symptomatic, we can be optimistic that it will effectively cure them," he said. But he still sees families who lose valuable time because the doctor who diagnoses their baby says that there is nothing that can help the disease. "My goal is to get the word out so that no patient experiences that delay," Day added. "It's critical."

Children with SMA-1 who receive nusinersen also continue to need neurological and pulmonary care, as well as extensive support—such as physical, occupational, speech and swallowing therapies—to ensure they continue to develop normally, he said.

Provided by Stanford University Medical Center