Deaf or Death? In Drug Trial, Parents Weigh Life vs. Hearing Loss

An experimental treatment could let children with a rare genetic disease live longer, but it may make them deaf

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Andrew Marella, 15, talks with his parents at the National Institutes of Health in Bethesda, Md., before getting his monthly infusion of cyclodextrin, an experimental drug being tested in a clinical trial of patients with the fatal ...

Andrew Marella waits before getting an infusion of cyclodextrin. The dose will be twice the amount of previous infusions, as researchers seek a dosage that will stop or slow the rare genetic disease. One side effect: the higher the dose, the greater the risk of hearing loss. *Lexey Swall for The Wall Street Journal*

Andrew Marella, right, is prepped for his cyclodextrin infusion. Every time a dose is increased, his parents, Phil Marella, seated, and Andrea Marella, standing next to Mr. Marella, must weigh the hope the drug will extend Andrew's life against the likely chance of hearing loss. *Lexey Swall for The Wall Street Journal*

Andrew Marella has a hearing test administered by Kelly King, an audiologist at the National Institutes of Health, who is monitoring the hearing of trial participants. Andrew's mother, Andrea Marella, waits. *Lexey Swall for The Wall Street Journal*

Andrew Marella, with his father, learned his hearing hadn't significantly worsened after the increased dose of cyclodextrin. *Lexey Swall for The Wall Street Journal*

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20 COMMENTS

BETHESDA, Md.—While waiting for an infusion of a drug that might save his life, 15-year-old Andrew Marella gripped the controls of an NFL videogame, the hand-held version of a sport he played when he could still run without fear.

Andrew is in a clinical drug trial of cyclodextrin, a sugar-based substance that scientists hope will stop or slow the progress of a rare genetic disease that kills most patients by the time they are old enough to vote.

There is a good chance cyclodextrin will extend Andrew's life. But his parents worry this will be the dose that leaves him deaf.

Families in the drug trial must decide whether to permit the higher doses of cyclodextrin that research shows might arrest the disease. Hearing loss is one side effect. "Deaf or death, what are our options?" said Andrea Marella, Andrew's mother. "We have to keep moving forward."

The National Institutes of Health launched the trial two years ago to test cyclodextrin in children with Niemann-Pick Type C—a cholesterol metabolism disorder known as NPC that has been diagnosed in about 200 people in the U.S.,

including Andrew. The trial, chronicled by The Wall Street Journal, initially tests the drug's safety.

All the children participating will likely lose some hearing, said Forbes D. Porter, the NIH doctor running this part of the drug trial. The higher the dose, the greater the risk, researchers found. But animals with NPC that were given cyclodextrin lived significantly longer than those untreated.

For the parents of the 14 patients in the trial, every infusion requires balancing the possibility of extending life against the near-certainty of a side effect that may hamper their children's few remaining years.

In mid-December, Phil Marella, Andrew's father, waited with his wife and son in a room in the NIH Clinical Center. Andrew was scheduled to get his first cyclodextrin infusion of 600 milligrams, a dose that has triggered hearing loss in other children receiving the drug and twice his dosage of a year ago.

'A logical trade-off'

"It's a risk we are willing to take if we can see the kind of success in children with quality-of-life and longevity that we have seen in cats," Mr. Marella said. "This is a logical trade-off."

He looked over at Andrew, who on the drive from their home in Greenwich, Conn., had been lobbying for a PlayStation 4. "You can rationalize all you want," Mr. Marella said. "There is still a moment of hesitation."

A day after receiving the higher dose, Andrew Marella entered a soundproof booth and put on headphones for a hearing test conducted by Kelly King, an audiologist at NIH who is monitoring participants in the cyclodextrin trial.

Andrew's mother sat at the back of the cramped room, her head down. She listened intently as her son repeated back words delivered to his headphones. Shawl, he said. Soup. When he finished, Andrew turned to smile at his mother and give a thumbs up.

“Hearing is such an important part of our quality of life,” Dr. King said. “It is a connection to the world.”

Parents of seriously ill children have told her that reading bedtime stories and lullabies are some of the remaining connections they share. “To risk taking that away is a big deal, especially when we don’t have proof yet that, in kids, cyclodextrin extends life,” Dr. King said. “It doesn’t mean it shouldn’t be done. But the consequences have to be acknowledged.”

Families often wrestle with the side effects of medical treatment. In cancer cases, for example, radiation can lead to permanent cognitive damage. And some drugs may cause a second cancer years later.

Clinical trials are especially complicated because a trial’s first phase is conducted to determine a drug’s safety and dosage, not whether it can help.

Hearing loss is already a symptom of NPC disease for many people that worsens as the disease progresses. Some parents don’t notice until their children are tested, Dr. King said. Minimal damage in the higher frequency ranges—either from the disease or the drug—may not affect conversation.

For many illnesses, it is ethical to enroll children in drug trials that risk side effects even if “there is little real chance of direct benefit,” said Yoram Unguru, a pediatric oncologist at the Herman & Walter Samuelson Children’s Hospital at Sinai in Baltimore.

Parents with sick children must decide whether to accept the trade-offs, said Dr. Unguru, who is also an ethicist at the Johns Hopkins Berman Institute of Bioethics. The question, he said, for families: ”Where do you draw the line? Is it hearing loss, renal failure, infertility, cardiac failure?”

The Food and Drug Administration and the NIH were told of instances of hearing loss and are allowing the drug trial to proceed because the potential benefits of cyclodextrin outweigh the risks, Dr. Porter wrote in an update Saturday to parents and others involved.

Andrew, a high school sophomore, has asked his parents about his chances. Mrs. Marella said they "try to keep it positive," with talk of future plans. Andrew's older sister, Dana, died from NPC disease in July 2013. Soon after, Andrew began having seizures, a symptom that could have been triggered by the stress of his sister's death, or a sign the disease had advanced. Now, Andrew is accompanied at school by an aide to watch for falls.

Andrew works hard to improve his gait and the clarity of his speech, both impaired by NPC. The trial, and the possible risks that go with higher doses of cyclodextrin, add more challenges to the teen's life.

Trying to fit in

Andrew likes to reel off scenes from the TV show "Big Bang Theory." When his older brother is home from college, the boys lift weights. "I have big shoulders," Andrew said.

More than anything, Mrs. Marella said, "Andrew wants to be like everyone else." After the seizures started, the family found Andrew a hat with a protective plate that looks like an ordinary baseball cap. At an age when teenagers insist on greater independence, Andrew can't be left alone in case he falls.

Andrew's parents asked the school to provide a young aide, someone they hoped might "seem cool," Mrs. Marella said, so other students would feel comfortable talking with Andrew. "He's buff," Andrew said.

Dr. Porter told Andrew the latest infusion might cost some of his hearing. Andrew later told his parents that he worried a hearing aid would make him look different.

After the hearing test, Dr. King told Andrew and his parents that the teenager's hearing was slightly worse. Andrew might hear the word "mouth" instead of "mouse," the doctor said, or "knife" instead of "nice."

In daily conversation, Andrew will likely pick up visual and contextual cues that will help him, Dr. King said. The change is so slight, she told Andrew, "I'm not surprised you haven't noticed."

Mrs. Marella was relieved. “Good job,” she told her son, “but that still doesn’t mean you get a PlayStation 4.”

Cyclodextrin first damages the ears’ outer hair cells, which function as an amplifier. Hearing aids can help. Researchers also found that high doses of cyclodextrin in cats and mice damage the ears’ inner hair cells, which may cause distortion of speech.

In such cases, Dr. King said, hearing aids don’t work. “Imagine blowing the speaker in your car,” she said. “No matter how much you turn up the volume, the sound is still distorted.”

It may be a while before science arrives at strategies to prevent or reverse the hearing loss known as ototoxicity, Dr. King said. The condition is also a side effect in such cancer drugs as cisplatin. Researchers at St. Jude Children’s Research Hospital recently identified a gene that makes some patients taking the drug more susceptible to hearing problems.

In the case of cyclodextrin, researchers are testing drugs that might mitigate hearing loss. That may not arrive in time to help Dr. King’s current crop of NPC patients—the ones, she said, “who keep me up at night.”

Based on animal research, Dr. Porter is convinced the children need still-higher doses to see significant benefits.

In January, some children in the trial moved up to 900-milligram doses, including Adam Recke, a 15-year-old Bethlehem, Pa., boy who has worn hearing aids since second grade.

The latest round of treatment worsened Adam’s hearing. Dr. Porter put the teenager on steroids and Adam’s hearing returned to where it was. But Dr. Porter warned the Reckes of possible health complications associated with regular steroid use. And Adam’s hearing might not continue to rebound.

Adam’s parents, Sean and Amy Recke, worry that one day hearing aids won’t help. “There are a lot of questions,” Mr. Recke said. “No one can give you answers. That makes it tough.”

Dr. Porter agreed the trial would be easier if everyone could be certain of the drug's benefits. In cats the drug helped most, he said, deafness is permanent: "I'm nervous."

In February, Adam got another 900-milligram dose and again suffered hearing loss. Doctors won't know until later this month if it is permanent.

Adam is eligible this month to try 1200 milligrams of cyclodextrin. After much discussion, his parents decided on a lower dose of 600 milligrams, afraid of further hearing loss. The prospect of making things worse, Ms. Recke said, "makes me really uncomfortable."

Andrew Marella expects to receive his first 900-milligran dose this month. "We can't wait for too long," Mr. Marella said.

When the parents ask for advice, Dr. Porter said, "I don't know if there is a right answer."

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Corrections & Amplifications

The name of the Johns Hopkins Berman Institute of Bioethics was incorrectly given as the Johns Hopkins Berman Institute of Ethics in an earlier version of this article. (March 2, 2015)

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