

Choosing to Enroll, or Not

Weighing the costs and benefits of joining an experimental drug trial.

BY JAMIE TALAN

Catie Allio was five years old in 1994 when she started to go blind. A few years later, the seizures began. At 11, she was referred to Candida Brown, M.D., a pediatric neurologist at Kaiser Permanente in California. Dr. Brown, who has since moved to Children's Hospital Oakland, looked at Catie's progressing symptoms and was certain she had the juvenile form of a rare, life-threatening condition called Batten disease. The neurologist had seen at least one other child with this form of the disease, and Catie's was a textbook case. The condition begins with failing vision followed by seizures, progressive loss of movement, and cognitive decline. Few children with Batten disease survive into adulthood.

BATTEN DISEASE

Experts say that there are not even 500 Batten disease patients worldwide. Ten forms of the disease exist, each caused by gene mutations. The most prevalent is a deletion in the gene *CLN3*, which causes the juvenile form that Catie has. *CLN3* is associated with a protein that helps lysosomes function. Lysosomes are small parts of the cells that can get clogged up with waste material and lead to damaged neurons in the brain.

Today, at age 21, Catie has lost about 90 percent of her vocabulary and much of her short-term memory. She is bedridden and gets her food and 21 daily pills through a gastric tube. But Catie's personality—cheerful, loving, and amused by just about anything—remains intact. She still believes in Christmas, and, in the few words she can now string together, she says that she sees angels.

Catie is the third of six children born to Kathy and Joe Allio. They live in Vacaville, CA. The year that Catie was diagnosed with Batten disease, the last of the Allio siblings—Annie, aged three—had a seizure. Her gait, or way of walking, was



TWO SISTERS' TRIALS Annie Allio (left, age 12) and sister Catie (age 21) both have Batten disease.

off just enough for Kathy and Joe to wonder whether she had the same disease as Catie. Then Annie's vision and memory started to deteriorate, and she had trouble learning the alphabet and numbers.

Annie is now 12 years old and has also been diagnosed with juvenile Batten disease. However, the course of her illness has been very different from Catie's. When Catie was 12, she was happily riding horses and learning Braille; in contrast, Annie has been plagued by mood disturbances since she was a toddler. Her obsessive behaviors have led to biting, scratching, hitting, breaking things, and high-pitched screaming.

Doctors say that her behavior is triggered by the progressive brain damage of Batten disease. She swallows 24 pills a day to control her seizures and behavior. Lithium, a drug for manic depression, has steadied her moods enough for her to smile, and she even started the school year recently.

THE PROMISE OF A NEW DRUG

The Allios recently learned of a trial for an experimental drug for Batten disease. The drug, mycophenolate mofetil (Cell-Sept), is federally approved for transplant patients and is now being tested at University of Rochester Medical Center for juvenile Batten disease.

In the 22-week Phase II trial—which primarily tests safety and tolerability as opposed to effectiveness—up to 30 children with Batten disease will be randomly placed into one of two groups for eight weeks: one group will get mycophenolate and the other a placebo. (See box, "Clinical Trial Phases," page 70.) At the end of eight weeks, all children will wait a month without taking either drug or placebo before being put into the other group for the remaining eight weeks. After the trial is done, researchers will compare groups to see if the children had more side effects while they were on

the medicine than on placebo.

“Families have been anxiously awaiting word on when we can launch this clinical trial,” says Frederick Marshall, M.D., associate professor of neurology at University of Rochester Medical Center. Funded by a million dollar grant from the U.S. Food and Drug Administration and the Batten Disease Support & Research Association (BDSRA; bdsra.org), the scientists have already received calls from 20 families inquiring about the study. It is open only to families with the juvenile form of the disease.

“We don’t expect that mycophenolate will reverse the disease, but we hope it will slow the onset,” says Jonathan Mink, M.D., Ph.D., professor of neurology, neurobiology and anatomy, and pediatrics and chief of child neurology at University of Rochester Medical Center and fellow of the American Academy of Neurology. “There is a fair amount of enthusiasm and hope, but there is no guarantee that it will work. If we knew it would work, we wouldn’t need clinical trials.”

A DIFFICULT DECISION

To be eligible for the trial, participants must be between 8 and 25 years of age and have a local physician willing to follow them closely throughout the study period. In addition, all participants must be able to walk 10 feet unassisted, which means that Catie would not qualify. Annie would. Each child will also need to make four trips to Rochester for evaluation and testing. However, the family isn’t sure they could control Annie’s behavior on the plane rides back and forth from California to Rochester or during her testing days there. What’s more, the drug works by suppressing the immune system, so it could make things worse for participants by lowering their body’s natural defense against infection. In addition, the disease may

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—KATHY ALLIO

be too far advanced for the Allio girls to benefit from the study.

But the most vexing question for the Allios is this: If the medicine stops or slows the disease process, would that mean a longer life of debilitating symptoms? “Would it be fair to stop this disease in its tracks?” asks Kathy Allio.

“Our decision process might be different if we had just received the diagnosis,” says Kathy. But Catie, who is at the end stage of the disease, now says only one or two words and has no motor skills. “Would we want to suspend her in this stage? No. Our family has a strong faith in God, and this helps us avoid seeing Batten disease as a tragedy.” By the time Annie was diagnosed, the family had mostly

decided to focus their energy, time, and money on quality-of-life issues instead of experimental treatments.

“We can help by giving Catie and Annie medicines for the symptoms, but we can’t save them,” says Kathy. “Annie has suffered so much with the behavioral symptoms. I would not be at peace leaving her in that place. Ethically, and as a mother, I couldn’t strand her on that island. It wouldn’t be fair.”

From the time of Catie’s diagnosis, the family has raised money for research. They understand why it is critical for families to join the study, even if their own children won’t directly benefit. “The only way to find a cure is to test promising medicines,” says Kathy. “Without people signing on to trials, there would be a stalemate with the disease,” Kathy says. “But each family has to make their own decision based on their unique circumstances.” Her husband, a minister and a lieutenant in the police department in Fairfield, CA, agrees. “This has become our normal,” Joe says.

A FATHER’S MISSION

Earlier this summer, Lance Johnston, executive director of the BDSRA, sent

Clinical Trial Phases

PHASE I: Researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

PHASE II: The treatment is given to a larger group of people to further evaluate its safety.

PHASE III: The treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely.

PHASE IV: Studies are done after the drug or treatment has been marketed to gather information on the drug’s effect in various populations and any side effects associated with long-term use.

a letter out to members of the organization telling them about the study and providing contact information for the Rochester researchers.

The challenge will be to identify patients early in the disease process. As Johnston knows, misdiagnosis is common. His daughter Lorena was 22 years old when she died of Batten disease. She was six when her vision started rapidly deteriorating, but ophthalmologists called it everything except Batten disease. At nine, the seizures began. A doctor finally got it right when Lorena was 14. She died in 1993, two years before the gene for juvenile Batten disease was discovered.

Since his daughter's diagnosis, Johnston has dedicated his life to fighting the disease. He spends a better part of each day speaking to parents of pediatric patients and reading every new study that is published. He knows every scientist in the world studying Batten disease.

Word of the mycophenolate study has spread globally. At an annual research and family support meeting held in July in Minneapolis, the team of researchers from the University of Rochester set up tables so that patients could go through a preliminary screening process. Among those answering questions and walking a measured distance was Sofia Martinez. At nine, Sofia is going blind. Sofia had been wearing glasses for years, but her eye doctor noticed a severe decline in her vision last February. Her prescription went from 20/60 to 20/400 in one month. Mark Pennesi, M.D., Ph.D., a genetic ophthalmologist at the Oregon Health and Science University, finally diagnosed Sofia with Batten disease in June.



PLAYFUL SPIRIT Sofia Martinez, age nine, is hoping to start a clinical trial.

And there they were a month later at the BDSRA annual conference in Minneapolis. Sofia, her six-year-old sister Isabella, and their mother live in the small town of Prosser, WA. The community held a fundraiser to pay the family's way to the meeting.

IN THE MEANTIME

After a long talk with Dr. Pennesi and the geneticists in Oregon, Sofia's mother, Rene Satterfield, sat down with Sofia and told her she has Batten disease.

"Sofia said, 'Oh, I have a disease.... Can I go out and play now?'" Satterfield recalls.

Her mother says that spunky spirit allows her daughter to take things in stride.

"She is facing a horrific future," Satterfield says. She knew that her daughter would meet children in all stages of the disease at the meeting. Most would be blind and unable to move at will. But she also knew that being around other families battling this disease would

make things a little easier.

Sofia was excited to make friends with a 12-year-old girl who holds a book up to her nose to see the pages, just like Sofia does. And Sofia asked if she could push her new friends in their wheelchairs.

"The whole experience was bittersweet," says her mother.

Sofia was tested for the Rochester study. "I am pretty hopeful that Sofia will be a candidate," her mother says. If Sofia gets into the study, she will be one of up to 30 Batten disease patients who will be given the immune-suppressing medicine.

For now, Sofia is doing what she knows how to do: be a little girl. She draws even though she no longer can distinguish between colors. She plays dress up. She acts in community plays. She gets dolled up for town pageants. This summer she even went to Hollywood through the Make-A-Wish Foundation.

She tells her mother that in the future she wants to travel to China to meet the child her family sponsors through an international relief organization. Her little sister painted a flower with the words "love is good" and the family made T-shirts to raise money for Sofia's care. (Isabella is not a carrier.) Their mother is navigating the Batten disease trail and figuring out how she can use assistive computer technology to help Sofia, who is now in fourth grade, see and communicate.

"Since this is a Phase II trial, it is all about establishing safety and tolerability," says Dr. Mink. He and his team have stressed to families "that there is no expectation of benefit."

Still, Satterfield says, "the study gives us hope for the future." ■