Opinion

My granddaughter's devastating rare disease deserves attention, too

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The Food and Drug Administration insists on large trials that show clear evidence of a drug's clinical effectiveness, meaning that symptoms improve or go away. But that doesn't make sense for rare diseases, writes the author. Pictured is FDA Commissioner Robert Califf testifying during a Senate Health, Education, Labor, and Pensions Committee hearing on Capitol Hill. (Manuel Balce Ceneta / AP, 2022) Less

By Christine Zahn
Special to The Seattle Times

Most kids don't like getting shots. But my 11-year-old granddaughter, Willow, recently asked her mom if she could start getting them again.

Willow was born with an ultrarare disease called arginase-1 deficiency. Between the ages of 1 and 3, children with ARG1-D may lose partial control of their legs and experience growth lags and muscle stiffness. As the disease progresses, patients develop severe intellectual disabilities, lose bowel and bladder control, and become unable to walk. Their average life expectancy is 40 years. Fewer than three of every million babies born are affected by this condition.

There's no approved treatment for ARG1-D. But in 2019, clinical trials began for a new therapy called pegzilarginase. At age 7, Willow joined one of those trials — and was transformed. Before, she could have as many as 30 seizures a day. After she started treatment, she had none. For the first time, she had normal levels of the amino acid arginine, the lack of which plays a key role in the disease.

She wasn't alone. More than 90% of those who received the drug in a randomized trial showed a lower blood level of arginine. Patients who received the therapy also showed improved mobility, and the drug posed no safety concerns.

The leading expert on ARG1-D — Dr. Stephen Cederbaum — supports pegzilarginase's approval.

In 2022, the drug's developer, Aeglea BioTherapeutics, applied for approval from the Food and Drug Administration. With such strong results, Willow's mom and I expected a speedy green light.

Instead, the FDA issued a "refusal-to-file" letter and declined to look at the trial data. Patients like my granddaughter lost the only hope they had.

The FDA insists on large trials that show clear evidence of a drug's clinical effectiveness, meaning that symptoms improve or go away.

But that doesn't make sense for rare diseases. By definition, there often aren't enough people suffering from each rare disease to populate a large clinical trial. Federal law defines a rare disease as one that affects less than 200,000 people. Diseases like ARG1-D could be considered ultrarare.

There are scientifically sound alternatives to clinical trials. If we understand the mechanism by which a disease operates, then we can evaluate the effectiveness of an intervention by measuring certain biomarkers associated with the disease.

The cause of ARG1-D is well understood. The body can't break down arginine, which builds up in the blood and cerebrospinal fluid and becomes toxic. The key to treating the disease is to reduce levels of arginine. Before pegzilarginase, the only way to do this was with a highly restrictive low-protein diet — and even that can only slow the disease, or lower the buildup of arginine by an insufficient amount.

But the FDA wanted to see clinical benefit in a randomized trial.

The pegzilarginase researchers managed to enroll 32 patients in their trial, an impressive number given how few people are affected by ARG1-D. And the trial did document a clinical benefit — improved mobility. But the difference fell just short of statistical significance. In response, the FDA claimed there wasn't enough evidence to demonstrate that high arginine levels cause ARG1-D in the first place.

The agency's denial has been devastating for patients. Aeglea was forced to close its ARG1-D program.

Without medication, my granddaughter has started falling more often, and her intense muscle cramps and brain fog have returned. Things are even worse for patients I know with more advanced cases.

The FDA needs to reconsider how it evaluates rare-disease drugs. In particular, it needs to start taking biomarkers into account. There's precedent for such a move. The agency has approved HIV and cancer drugs based on biomarkers.

Willow is old enough to understand what's happening. She knows she was sick, that the shots made her better, and that without her shots, she's sick again. What she can't understand is why the FDA would cut her off from treatment. I tell her that I can't understand, either.

***Christine Zahn** is the founder and director of the Arginase 1 Deficiency Foundation and grandmother of an 11-year-old with the disorder.*

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