Will short-term and long-term treatments for single-gene diseases survive?

May 22 2017, by Ricki Lewis, Phd

Two weeks and several political disasters ago, the House of Representatives passed the American Health Care Act of 2017, and soon lists of "pre-existing conditions" festooned news feeds. We all ticked off a few. But the lists, although acknowledged as incomplete, offered a highly inconsistent menu of maladies as broad as "cancer" yet as specific as "cystic fibrosis." I don't know whether the focus on the familiar reflects editorial choices to appeal to the masses, or ignorance of or deliberate avoidance of mentioning many of the lesser-known rare diseases. More than 30 million people in the US have rare diseases, many of them genetic and some of those treatable with approaches more complex than those used for more common conditions.

Last week DNA Science addressed the possibility of the AHCA forcing pregnant women to carry doomed fetuses to term, the discussion now in the hands of 13 senators, whom I suspect have never been pregnant. This week I fear for the treatments for single-gene conditions, both the short-term and available protein-based ones as well as the not-yet-approved gene therapies. So here's a brief look at two ways to counter errant single genes.

ENZYME REPLACEMENT THERAPY

Last week between crises CNN.com told the remarkable story of recent college grad Ryan Dant. Born in 1998, Ryan seemed healthy until a routine check-up at age 3 revealed a liver and spleen twice normal size. That led to diagnosis of a form of mucopolysaccharidosis (MPS), a class of devastating inborn errors of metabolism (the lysosomal storage diseases) in which specific sugar-like molecules accumulate in many tissues, including the brain, due to a missing enzyme. May 15 was MPS Awareness Day.

Ryan wasn't expected to survive beyond age 10, but entered a clinical trial for an enzyme replacement therapy (ERT), what would be named

Aldurazyme, in 1998. It won FDA approval in 2003 and Ryan still has the four-hour, weekly infusions of the drug he needs to live. It costs about $200,000 a year; I found a discounted price of $865.82 at CVS with an online coupon, and some quick math revealed that this is likely for one infusion.

So ERT is expensive. One of the first, Adagen, to treat severe combined immune deficiency due to adenosine deaminase deficiency (SCID-ADA), was FDA-approved in early 1990, and treated 19 children the following year, for $100,000 to $350,000 each. More recently, Baby Etienne's parents told their story, thanking Canada's newborn screening program for adding SCID-ADA to the standard panel. Etienne's Adagen costs $10,000 a week, adding up to $520,000 a year. It's a once or twice weekly injection.

The high cost of lifelong frequent infusions or injections of ERT is why the "forever fix" of a gene therapy is an attractive alternative, even if a booster or two becomes necessary. Gene therapy delivers the DNA instructions for making the missing enzyme. Another reason to seek gene therapy (or editing) is that enzyme infusions don't reach the brain.

Theoretically, gene therapy should be more economical than ERT, once research costs have been recouped. Barry Byrne, MD, PhD, from the Powell Gene Therapy Center at the University of Florida, explained the regulatory reasoning at a meeting on gene therapy at the New York Academy of Sciences May 11: "Of 10,000 compounds investigated, 250 might get to preclinical trials, and 5 into clinical trials, to get one FDA-approved drug. If you realize a gene can be a drug and that single gene is the cause of the disease, you can eliminate that discovery period, the clinical trial shortened, and overall the concept of genes as medicine is becoming reality." But the hurdles are still quite high, and even regulatory approval isn't a sign of sustained success (see Pulling the Plug on the First Gene Therapy Drug here a few weeks ago).

ERT and gene therapies have evolved in tandem, since the mid-1980s. Both work; one researcher compares them to the co-existence of standard toothbrushes and the electric variety. The two approaches echo the "central dogma" of genes encoding proteins: each is a point of potential intervention.

By enabling patients to live longer, ERT can reveal unknown manifestations of a disease, perhaps providing new drug targets or suggesting uses for existing drugs. And new ERTs continue to be approved – a recent one was for a form of Batten disease (late infantile neuronal ceroid lipofuscinosis type 2). Yet the first FDA approval for a gene therapy has yet to happen. One reason may be the relative complexities of the two strategies. I put gas in my Prius every few weeks – like ERT – but I wouldn't mess with the car's computer controls – like gene therapy.

Encouraging news from a gene therapy trial is incremental, for many reasons.

- Single-gene conditions tend to be rare
- Gene delivery systems are painstaking and costly to create
- Assessing progress entails comparison to detailed natural history studies that chart the course of the illness

Last week at the annual meeting of The American Society of Gene and Cell Therapy, Abeona Therapeutics discussed interim findings for their clinical trial to treat Sanfilippo syndrome type A, aka MPSIIIA, a different form of the disease from what Ryan Dant has. So far Abeona has treated two cohorts of kids, the first three children receiving 5 trillion adeno-associated viruses (AAV9) carrying the healing gene per kilogram of body weight and the second trio getting twice the dose. The researchers reported on the first 5 kids.

Eliza O'Neill, treated May 10, 2016, is part of the first cohort, and just yesterday she completed her one-year evaluation at Nationwide Children's Hospital in Columbus, Ohio. DNA Science has covered Eliza's journey in many posts, most recently here. She received a one-time intravenous injection into a vein in her hand. AAV9 crosses the blood-brain barrier, enabling a less invasive delivery than directly into the brain, as past clinical trials have done.

Eliza and Ryan's diseases directly affect the lysosomes, the sacs in cells that house enzymes that chew up specific molecules. Disable or remove any of the 43 types of lysosomal enzymes and the substance it normally breaks down instead builds up. For kids with Eliza's form of the disease, heparan N-sulfate builds up.

Like Ryan, Eliza had a few years of good health. Results of the recent natural history study pinpointed the start of the rapid decline for her disease: around 30 months.

"About 70% of the kids don't reach the age of 18, due to the profound deficiency in the lysosomes, which are the garbage factories of the cell. And when an enzyme that breaks down one sugar in the cell is deficient, the entire metabolome shows effects," explained Abeona CEO and president Tim Miller, PhD on a conference call from the meeting last week. He was referring to a mouse study on a different form of MPS that showed that a glitch in one lysosomal enzyme type has ripple effects on others.

Treating kids with either of two doses revealed a possible dose-response, Dr. Miller reported.

Specifically, levels of heparan sulfate in the cerebrospinal fluid and the sizes of the liver and spleen went down in both cohorts, as nonverbal IQ scores either stabilized or increased in the first cohort (the second hasn't

been post-treatment long enough to tell). So far there's no evidence of immune rejection. Some of the changes began earlier and more dramatically among the higher-dose children. "With the increased dose in cohort 2, we see a 2.5-fold increase in reduction of heparan sulfate in the cerebrospinal fluid and a drop in heparan sulfate of 6%," Dr. Miller said.

Importantly, the kids in the first cohort are ages 4.2-6.5; those in the second cohort are 2 to 4. The natural history study will be able to parse any effects of age and dose. But there's evidence for other lysosomal storage diseases that treating before the brain is damaged is best. And of course the sample so far is tiny.

Still, one year out, there's a sense of optimism about gene therapy for Sanfilippo, although "it's too early to make any conclusions," says Glenn O'Neill, Eliza's dad. And even though only a few kids have been treated, results so far have enabled the researchers to utter, albeit hesitantly, such phrases as "potential functional cure" and "disease modification." It's a start – one that I hope will help the parents who post on Facebook when either their diagnostic odysseys lead to an MPS, or they learn about it suddenly, as Ryan Dant's parents did when they took their seemingly healthy 3-year-old for a well child checkup.

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