Three gene therapy trials report good news

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"When you hear hoofbeats, think horses, not zebras," beginning med students learn. Ultrarare diseases are more like unicorns.

The rarity of many single-gene diseases complicates design of clinical trials of any type of treatment. How can researchers recruit a control group, when only a handful of patients has the condition? Many of these conditions affect very young children.

Paired parts, like eyes, can perhaps be treated at different times in the same individual and responses compared. For neuromuscular conditions, affected siblings can be treated at different times, which raises bioethical issues no matter how it is done. Treat the healthier, younger sib first because the chances of success are greater, or the sicker older sib first because the situation is dire and results can help the younger child later? The recent article in MIT Tech Review, Gene Therapy Trial Wrenches Families As One Child's Death Saves Another," tells it all in the headline.

Progress must be meticulously charted against the "natural history" of the disease, which must either be well established, as it is for Duchenne muscular dystrophy (DMD), or tracked before the start of a clinical trial, as happened for giant axonal neuropathy (GAN). Parental observations overlay natural history. A few extra steps for a boy treated for DMD might fall within the realm of what is possible for that disease among all patients, yet be extraordinary for him.

It's best to cover all bases in assessing progress. That's why the clinical

trial for gene therapy to treat GAN has a primary 8-week outcome of safety, but also a list of secondary outcomes: improvement in pathology, histology, physiology, function, and clinical markers, such as the dissipation of a build-up that indicates the reawakening of an enzyme.

Clinical trials may induce some degree of not quite a placebo effect on parents, but a lifting of depression and perhaps energizing at the possible ending of desperately watching a child decline and the first glimmers of hope that things may turn around. An overnight response is unlikely, perhaps more parental wishful thinking than biological change. That's why clinical trials for gene therapies typically stretch a decade or longer for follow-up.

With that background, I'll check in with a few of the trials that I follow.

Hannah

Hannah Sames with Steven Gray, PhD, who developed the gene therapy that she received days earlier.

It's much too soon to tell whether the gene therapy that 12-year-old Hannah Sames had last month for GAN is having an effect. Hannah returned to the Children's Inn at NIH a few days after the introduction of the gene-carrying viruses into her cerebrospinal fluid (CSF) to a huge pile of cards and gifts.

While everyone awaits the tests and measurements that may hint at efficacy, Hannah has been busy with rehab, reports her mother Lori, who posted a video on Facebook of her daughter throwing a kiss: "We've been working every muscle group, including face and lips. Turn on the volume and hear that pucker!"

Lori hopes Hannah's increasing strength reflects motor neurons producing the gigaxonin protein that her two deleted genes make impossible, and not just the prednisone prescribed to dampen her immune response.

Perhaps Hannah's disease will slow or stop, and she may even regain some feeling in her legs. While her parents and providers wait and see, and she remains with the other GAN warriors for a few more weeks, Hannah has had a few days off from muscular function tests to visit the nation's capitol.

Pfizer just announced its acquisition of gene therapy company Bamboo Therapeutics, which is developing the gene therapy for GAN as well as for Duchenne muscular dystrophy, Canavan disease, and Friedreich's ataxia.

"Hannah is doing great!" reports Lori, who can't really say much more at this early stage other than that the treatment appears to be safe. But she and everyone else is hoping that within 6 months, the aggregates of deranged intermediate filaments filling the motor neuron axons snaking down Hannah's legs will begin to dissipate, as they do in the mouse model, and Hannah makes regulatory T cells for gigaxonin, heralding immune tolerance.

Eliza

Glenn and Eliza O'Neill

Eliza O'Neill is only about 2 months ahead of Hannah, but already biochemical signs and perhaps observations suggest that her gene therapy is working. Eliza has Sanfilippo syndrome type A (aka mucopolysaccharidosis Type IIIA or MPS IIIA). DNA Science has followed the story of her parents keeping her at home the past two years to avoid infection with the virus used to deliver the gene therapy.

In Sanfilippo syndrome type A, the cellular suicide sacs, the lysosomes, swell with a compound called heparan sulfate, due to an enzyme deficiency. Children lose neurological skills, yet are hyperactive and do not sleep very much. Eliza can no longer recite the alphabet, sing, or

even let her parents know when something hurts. She is the first child to receive the gene therapy in a vein (in her hand). So far she's done so well, in terms of safety, that a second child has been treated.

Another trial for Sanfilippo type A, conducted in France by the company Lysogene, started in 2011 to deliver the gene directly into the brains of 4 children. This video tells the story of Karen Aiach, an accountant who founded Lysogene to develop the gene therapy, which her daughter Ornella received, like Eliza, at age 6. According to the film, Ornella's behavior calmed dramatically after the gene therapy.

Eliza's parents are noticing a difference too since the gene therapy. They try to be objective, but that's hard when they've watched their little girl fade away, losing all ability to communicate.

"Since treatment, we see a new light in Eliza's eyes— she is connecting with us in a way we thought was gone forever. She is working to regain the skills the disease stripped away in the 6 and half years it tore through her body. She is a fighter!" said her father Glenn. For an update see this video. Adds Eliza's mom Cara of other affected children, "We have to help them. We can't leave them behind."

The O'Neills, who founded the Cure Sanfilippo Foundation, are doubling their efforts, attempting to raise $4 million to treat more youngsters. And they are thrilled that People magazine has covered their quest, with an update in this week's issue, as has The Today Show.

Biochemical findings back up what Glenn and Cara hope they are seeing. Abeona Therapeutics, the company sponsoring the clinical trial, recently announced "encouraging early biopotency signals" that suggest a reduction of the biochemical buildup in the urine and CSF, as well as potential disease-modifying effects in the liver and spleen, hinting at a body-wide effect. Stay tuned.

Seeing the Light

Corey Haas owes his vision to gene therapy

The gene therapy that I wrote my book about, to treat "inherited retinal disease due to mutations in the RPE65 gene" (aka Leber congenital amaurosis type 2), is so far along the regulatory trajectory that it has its own unpronounceable name: voretigene neparvovec. The treatment, from Spark Therapeutics, could go down in history as the first FDA-approved gene therapy in the US.

A recent article in The Lancet reports safety and efficacy for a continuation of the phase 1 trial 3 years after patients were treated in their second eyes. The company also reports results of a phase 3 trial that treated 20 initial patients in both eyes, with a control group of 9 people who were treated in both eyes a year later. Eight of the nine achieved about 200-fold improvement in visual acuity, with no adverse events, as did the original 20.

Meanwhile, the 8-year-old who had his vision restored who inspired my book will soon turn 16! "Corey worked this summer for the town of Hadley as grounds keeping, so he got to pick up the town parks, cut brush and clean up at the town garage," reports Nancy Haas, his mom.

Too Late For Some

Taylor King

Even more inspiring than the families who have made gene therapy possible for their own and other children are those that do so even when gene therapy, or anything else, will be too late for their own children. That's the case for the family of Taylor King, who turns 18 tomorrow. Happy birthday Taylor!

Nowadays there is a lot that Taylor cannot do. But her legacy will be to help others – the research team behind Hannah's gene therapy for GAN will next tackle Taylor's disease, neuronal ceroid lipofuscinosis, the infantile form of Batten disease.

Taylor's older sister Laura is running a race in every state to spread the word about the need to develop a treatment for Batten disease, and her mother Sharon, is a very vocal advocate for the rare disease community. The organization that the family founded, Taylor's Tale, is funding the gene therapy research and helped to establish an Advisory Council on Rare Diseases within the School of Medicine of the University of North Carolina at Chapel Hill, which was signed into law a year ago.

I am in awe of all of these families and feel honored to know some of them.

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