Investigational drug evaluated in newborns to treat rare disorder

March 21 2014, by Elizabethe Holland Durando

Robert and Sarah Yaroch visit their son Andrew in the neonatal intensive care unit (NICU) at St. Louis Children's Hospital. Andrew is the third baby worldwide to participate in a clinical trial to treat a rare genetic disorder called X-linked hypohidrotic ectodermal dysplasia (XLHED). Credit: Elizabethe Holland Durando

Children with a rare genetic disorder that causes missing and malformed teeth, sparse hair and the inability to perspire are born without a protein

thought to be key to such development.

A clinical trial now underway at Washington University School of Medicine in St. Louis aims to see if the void can be filled with replacement-protein therapy.

Kathy Grange, MD, professor of pediatrics at Washington University, is treating a baby boy with the disorder at St. Louis Children's Hospital. The baby, Andrew Yaroch of Waterford, Mich., is only the third child in the world to receive the drug to treat X-linked hypohidrotic ectodermal dysplasia (XLHED).

The first two infants to participate in the Phase 2 trial received their treatments in California and Germany.

The treatment involves giving EDI200, a replacement protein, to newborn boys found to have mutations in the EDA gene. Individuals with the disease can't produce a protein, ectodysplasin A, that is important in the development of hair, teeth, and exocrine glands such as sweat and salivary glands, which use ducts to secrete their products.

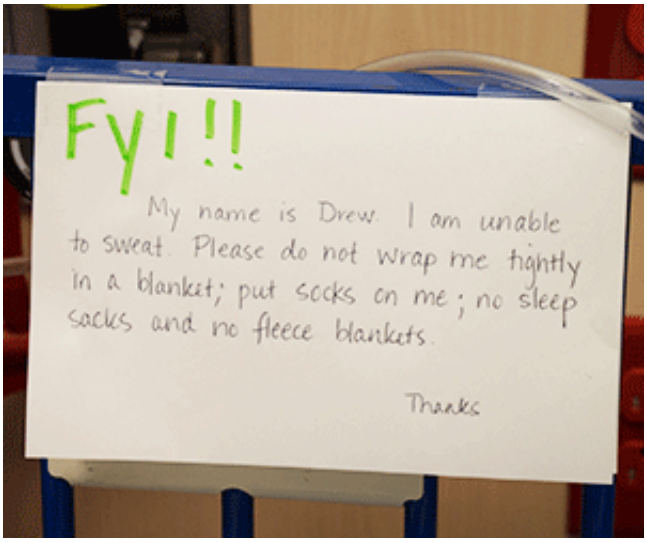
There are currently no treatment options for the disease, other than supportive care.

One of the challenges for investigators is that infants with the disease need to be diagnosed shortly after birth because the intravenous drug treatments are believed to be most effective if begun before the child reaches two weeks of age. The trial calls for a total of five doses of the replacement protein, the first of which is given in the first two weeks of life, and the remaining four doses over about a two-week period.

Only boys are included in the trial because they are afflicted with XLHED more often and more severely than girls. The disorder is caused

by a defective gene located on the X chromosome. Females get two copies of the chromosome—one from each parent. So if the XLHED gene is faulty on one X chromosome, the healthy version of the gene on the other chromosome compensates. Males, however, only have one X chromosome, and if the XLHED gene is defective, they inherit the disease.

Andrew was born Feb. 20 in Michigan to Sarah and Robert Yaroch and was quickly diagnosed via genetic testing because of his parents' familiarity with the disease. While Andrew has two older siblings who don't have XLHED, a cousin and his maternal grandfather do.



A sign in Andrew's hospital crib alerts staff and visitors to his inability to sweat. Credit: Elizabethe Holland Durando

The family learned of the clinical trial from Sarah Yaroch's sister, whose 6-year-old son has the disorder. She linked the Yarochs to the National Foundation for Ectodermal Dysplasias, based in Fairview Heights, Ill., and the nonprofit organization connected the family with researchers

conducting the trial.

Andrew and his parents flew to St. Louis earlier this month, in time to begin the treatments March 5, at 13 days of age.

"I knew that this was what we needed to do," said Sarah Yaroch. "We knew that this was what was best for him in the long run, whether it has the desired effect or not. My grandkids could have this, my daughter could be a carrier, and it needs to be researched. I feel like we need to help somehow."

Added her husband, Robert Yaroch: "Not everybody has an opportunity to have an impact on the world at large, so I think this is best for Drew, best for our family, best for our extended family—and for other people who could have it in the future and be helped by this."

An international team including then-Washington University researchers David Schlessinger, PhD, and Anand K. Srivastava, PhD, identified the gene for XLHED in the mid-1990s, making research to treat the disorder possible.

Edimer Pharmaceuticals, based in Cambridge, Mass., developed the replacement protein and is funding the trial. Edimer has reported that studies involving XLHED-affected mice and dogs have resulted in permanent corrections regarding some of the disease's manifestations.

The company estimates that worldwide, five in every 100,000 boys are born with the disease. Further, about 50 percent of girls who carry the genetic defect have symptoms that would warrant therapeutic intervention.

XLHED is rare but is one of the most common forms of ectodermal dysplasia.

"Males are much more significantly affected than females," Grange said, explaining why the trial targets newborn boys. "The gene defect they have results in the inability to make a signaling protein that is needed during development of the teeth, hair, sweat glands and other exocrine glands of the body."

People with XLHED are at risk of hyperthermia because of their inability to regulate body temperature. Many also experience recurring respiratory infections.

Those with the disorder also may have eczema, asthma, chronic sinusitis, recurrent nosebleeds and dry eyes. They also typically require significant dental interventions, such as dentures and implants, beginning at a young age.

The researchers believe that the earlier treatment is initiated, the better the outcome may be.

"Maybe in the future the treatment ideally would be given prenatally, but at this point we're trying to give it as early as possible after birth," Grange said.

Provided by Washington University School of Medicine in St. Louis