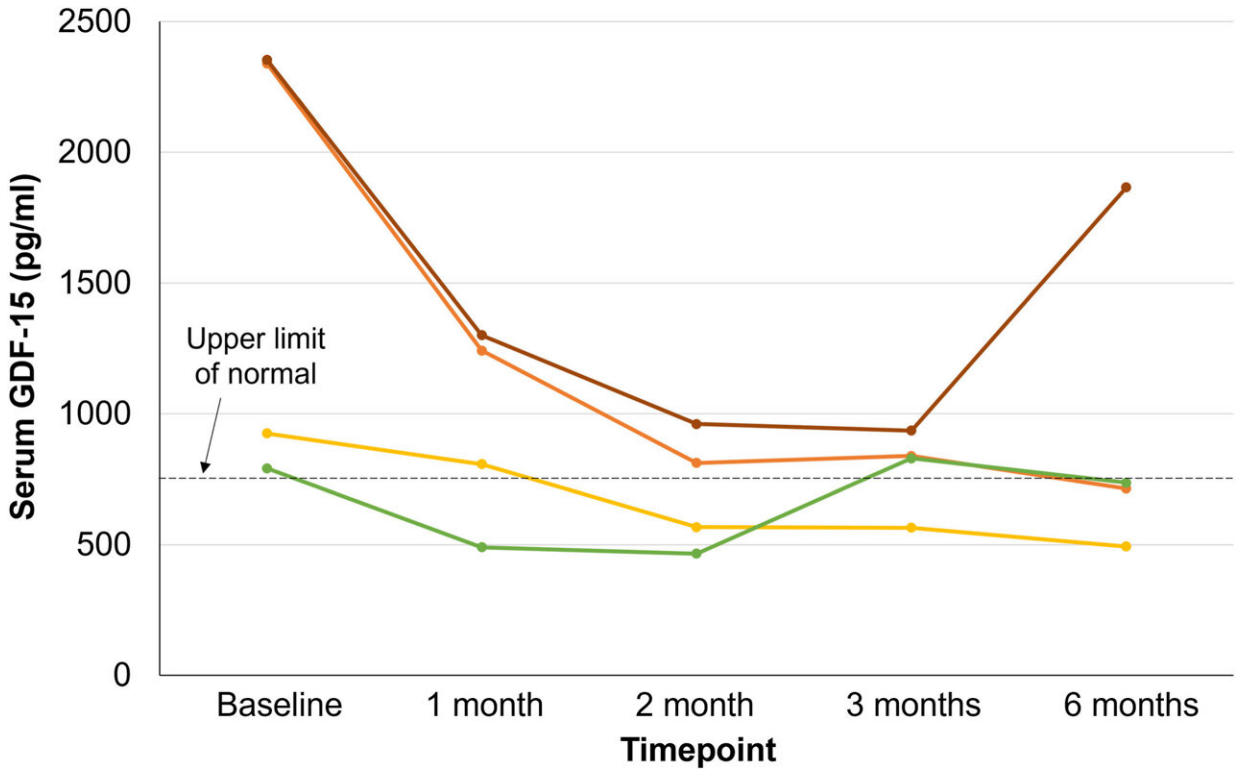
First-ever effective therapy for rare, devastating neurodegenerative mitochondrial diseases

July 29 2024



Serum growth differentiation factor 15 (GDF-15) over time in patients with elevated baseline levels. Each patient is represented by a different color line. Credit: *eClinicalMedicine* (2024). DOI: 10.1016/j.eclinm.2024.102740

A new treatment could improve the lives of patients with mitochondrial

diseases called POLG-related disorders, according to a unique clinical trial led by the Research Institute of the McGill University Health Center (RI-MUHC). Patients affected by these disorders experience progressive neurological decline and have a median survival of five months after onset of symptoms.

The preliminary results from the Phase 2 open label clinical trial, published in *eClinicalMedicine*, showed that Deoxycytidine/Deoxythymidine Combination Therapy is a safe and potentially effective treatment for POLG-related disorders.

"Our study gives new hope to affected families around the world, as a diagnosis of a POLG-related disorder involves regression in the child's motor and cognitive development and was previously a death sentence," says Dr. Kenneth Myers, a pediatric neurologist at the MCH and a researcher in the Child Health and Human Development Program at the RI-MUHC.

"The study treatment is not a cure, but the clinical status of the patients in our cohort is much better than would be expected, knowing death often occurs only a few months after symptom onset. The patients in our cohort are not only alive, they are doing better."

Fixing the body's power stations

Mitochondrial diseases are characterized by dysfunction of the mitochondria, the cellular organelles that produce the energy that human cells need to function normally. Worldwide, an estimated 1 in 5,000 people has a genetic mitochondrial disease.

In POLG-related disorders, mutations in the POLG gene cause a reduction of mitochondrial DNA content (mtDNA), which is essential for normal mitochondrial function. This leads to a range of signs and

symptoms that can include seizures, vision loss, muscle dysfunction (myopathy), nerve damage (neuropathy), developmental impairment or regression, and liver failure.

The investigative therapy, which has been used previously for a different mitochondrial disease, targets the defective genetic mechanism that leads to mitochondrial DNA depletion.

After six months of treatment, the patient scores on the Newcastle Mitochondrial Disease Scale—a validated clinical scale used to assess the progression of mitochondrial disease—were lower, suggesting therapeutic efficacy. The researchers also report a decrease in serum growth differentiation factor 15 (GDF-15) levels—a quantitative biomarker of mitochondrial dysfunction.

Finally, caregivers of POLG patients reported clinical improvement, including in energy level, motor function, cognitive status and communication. No serious adverse events attributable to the treatment were reported.

"Many of the patients in the trial were doing well and developing quite normally, until they contracted an infection or experienced another POLG disease triggering event and regressed completely, losing their ability to walk, speak or eat. It's really devastating for the family when that happens," explains Dr. Myers. "With this drug, we're giving patients the mitochondrial DNA building blocks they lack, to help their mitochondria produce the energy their cells need to function properly."

"One patient was asymptomatic until the age of 15, when her condition began to deteriorate. She started having seizures and had weakness and balance issues so that she could only walk a few steps on her own. Since starting the trial, she is no longer using a wheelchair and is essentially living the life of a normal teenager," adds Dr. Myers.

The new publication reports results from the first 10 children and adolescents with POLG mutations enrolled in the trial, some of whom traveled from the United States, Brazil and India to join it. All of them received the same treatment, Deoxycytidine/Deoxythymidine in three oral portions per day, for an initial period of six months.

The treatment period was extended to 24 months after some participants had significant positive responses and wished to continue on the therapy. An additional 14 POLG patients have since enrolled in the trial, and a follow-up publication describing the longer-term effects in a larger cohort is being prepared.

Liam's story: When life takes a turn

Liam is a ten-year-old child with mitochondrial disease caused by mutations in the POLG gene.

In May 2019, Liam started to have some seizures and was brought to the MCH. He stayed there for about five weeks, having seizures almost 24 hours a day until he got the right mix of medication. When he went back home, he had lost all ability to communicate. Shortly after, in June 2019, he started to have a few more seizures and was readmitted to the hospital. That's when genetic test results came in and the POLG diagnosis was made.

"When Liam was diagnosed, we were told his condition would worsen over time, and that he would lose his life to this disease. This news has crushed our family and it has changed the path of my life," says Liam's father, Kevin Reason, who has since devoted himself to the cause.

Dr. Myers told him about Deoxycytidine/Deoxythymidine, a new treatment that could possibly help Liam, and together, they decided to initiate a clinical trial. Kevin started the Liam Foundation to fund it.

"Today Liam is able to walk again, he is able to communicate and he smiles. All we see is improvement," says Kevin. "We know this treatment is not a cure, but it's giving us hope. And it's buying us much needed time, the time that we need to find a cure."

Liam was the first POLG patient to try the treatment in North America. Thanks to the Liam Foundation and additional support from other nonprofit organizations, 23 other POLG patients have since enrolled in the clinical trial.

More information: Heather Pekeles et al, Safety and efficacy of deoxycytidine/deoxythymidine combination therapy in POLG-related disorders: 6-month interim results of an open-label, single arm, phase 2 trial, *eClinicalMedicine* (2024). DOI: 10.1016/j.eclinm.2024.102740

Provided by McGill University Health Centre