New Therapies Being Developed for Batten Disease at 'Unprecedented' Pace, Review Suggests

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Alejandra Viviescas March 29, 2019

Substantial progress has been made by different academic and industry teams toward the development of effective therapies to treat Batten disease, a review study suggests.

In addition, many of the research strategies being explored for one form of Batten might be useful for other Batten types and even other disorders.

The study, "Therapeutic landscape for Batten disease: current treatments and future prospects," was published in *Nature Reviews Neurology*.

Batten disease (also known as neuronal ceroid lipofuscinoses) is a group of genetic neurodegenerative disorders that cause a progressive decline in motor and cognitive abilities. There are fourteen types of the disease (CLN1-CLN14) caused by mutations in different genes. All these mutations lead to abnormal storage of lipids in cellular compartments called lysosomes.

Researchers seeking to develop new Batten disease therapies faced the problem of not knowing the exact function of the proteins that are affected by these disease-causing mutations. However, in recent years, different animal models for Batten have been developed to address this question.

The use of mouse models for different types of Batten has accelerated the testing and preclinical development of targeted therapies. There are some significant differences between human and mice, however, which can be overcome by using bigger animals — especially pigs

whose brain development is very similar to that of humans — as Batten disease models.

Enzyme replacing therapy

Enzyme replacement therapy (ERT) can help treat Batten disease by replacing a patient's missing or deficient enzyme with a fully functional one. This can help restore the proper breakdown of waste material within cells, and prevent cell death.

ERT can only be used in Batten types where the affected enzyme is soluble, because the therapy needs to cross the blood-brain barrier (a semi-permeable membrane that protects the brain) to effectively reach the brain. These types includes CLN1 (infantile Batten), CLN2 (late-infantile Batten), CLN5 (also known as Jansky-Bielschowsky disease), and CLN10 (congenital Batten).

In 2017, Brineura (cerliponase alfa), an ERT developed by BioMarin for the treatment of CLN2, became the first specific therapy for Batten disease to be approved by the U.S. Food and Drug Administration.

Gene therapy

Most gene therapies take advantage of a mechanism naturally developed by a specific virus, called an adeno-associated virus (AAV), that allows it to insert fragments of DNA into the human genome.

Using inactivated viruses as carriers (AAV vectors), researchers can insert a functional copy of a mutated gene into patients' cells. This strategy has been shown to be safe and effective for different neurodegenerative disorders.

The first Phase 1 clinical trial (NCT00151216) testing a gene therapy in children with CLN2 disease started in 2004 and is estimated to finish later this year. Preliminary results showed that the treatment was well-tolerated, had no significant side effects, and caused a slight reduction in the speed of neural decline.

Two ongoing clinical trials (NCT01161576 and NCT01414985) are testing the same gene therapy using a new, optimized version of the AAV vector to achieve widespread distribution of the treatment and therefore a more significant response.

Amicus Therapeutics is currently sponsoring two trials in Ohio involving patients with different forms of Batten disease. The Phase 1/2 open-label clinical trial (NCT02725580), expected to finish later this month, is testing the effects of one-time intrathecal administration (injection directly into the spinal canal) of the *CLN6* gene in 12 patients with CLN6 Batten disease.

The other Phase 1/2 clinical trial (NCT03770572) is currently recruiting subjects with CLN3 Batten to test the safety and efficacy of a one-time intrathecal administration of the *CLN3* gene.

Stem cell therapy

Stem cell therapy consists of implanting cells that have the potential to transform into functional neuronal cells, which then secrete the enzymes missing in Batten patients in order to slow, stop, or reverse disease progression.

A Phase 1 clinical trial (NCT00337636) in Oregon involved implanting healthy neuronal stem cells into CLN1 and CLN2 Batten patients. The implanted cells were supposed to produce a significant amount of the proteins lacking in these disease subtypes. Although the treatment was well-tolerated and cells survived inside the patients for more than a year, it failed to ease the symptoms and progression of the disease.

Small-molecule therapy

Small molecules include compounds that can improve lysosomal function, modulate the immune system, or serve as neuroprotective agents.

The use of chaperones — small proteins that fold other proteins into their functional state — and agents that reduce degradation of non-functional proteins have shown promise in a preclinical setting but have not yet reached the clinical testing stage.

There appears to be an autoimmune component in Batten disease. Therefore, medicines that alter the immune system (immunomodulators) seem to play a role in disease progression.

A Phase 2 trial (NCT01399047) evaluated the safety, tolerability, and effect of the immunomodulator mycophenolate mofetil in children with CLN3. The compound was well-tolerated but showed little efficacy. Its administration over a more extended period might have yielded better results.

In complex diseases such as Batten, therapies that address multiple aspects of the disease at the same time have the potential for higher impact than those focusing on one aspect.

“The use of several treatment strategies might offer additional benefits to patients with neurodegenerative disease, but the benefits of this approach must be weighed carefully against the additional adverse effects that combined treatments might bring,” the researchers wrote.

The team also noted that “over the past two decades, scientists and clinicians within the Batten disease community have worked to ensure that tools are in place to enable progress towards effective treatments at an unprecedented pace.”

Recent progress in Batten disease research offers hope that efficient and targeted therapies will be available soon, the researchers said, noting that the “Batten disease research community is becoming a model of how effective, efficient rare disease research can be accomplished by working together.”