GENETIC THERAPIES FOR HUNTINGTON'S DISEASE FAIL IN CLINICAL TRIALS

Hopes were high for drugs designed to lower levels of a mutant protein, but development has stalled.

By Diana Kwon

Two pharmaceutical companies have halted clinical trials of gene-targeting therapies for Huntington's disease (HD), following the drugs' disappointing performance.

Researchers had hoped that the treatments – known as antisense oligonucleotides (ASOs) – would be a game changer for HD, an incurable genetic condition that affects cognition, behaviour and movement. But back-to-back announcements from Roche, headquartered in Basel, Switzerland, and Wave Life Sciences, in Cambridge, Massachusetts, have dealt a crushing blow to those affected by the disease.

"I was really shocked, really tearful," says Marion, a woman in London with HD, who was part of one of the trials. "We didn't see it coming at all. I felt really frightened and worried about my future." Marion requested that her last name be withheld to protect her privacy.

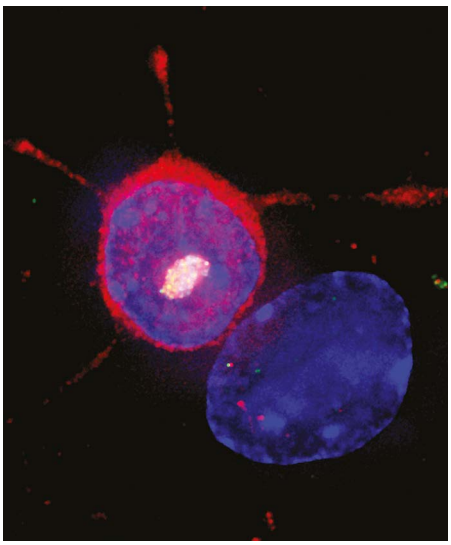
In mid-March, Roche announced that it was halting a phase III study of its ASO drug, tominersen. A week later, Wave Life Sciences said that it would discontinue the development of two of its HD ASOs that were in phase I/II clinical trials.

"The Roche trial in particular left the community quite devastated," says Cath Stanley, chief executive of the Huntington's Disease Association, a UK advocacy group supporting people with the disease. "There has been so much positive noise around it, both from researchers and clinicians and from the drug company themselves. I think the community was really swept up by that hope."

Problem proteins

ASOs are short strands of DNA or RNA that modify the production of specific proteins by binding to sequences of RNA made by faulty genes. The gene involved in Huntington's codes for a protein called huntingtin that is active in the brain. In people with HD, this gene repeats a short piece of its sequence – the nucleotide combination CAG – too many times. Both Roche and Wave Life Sciences were developing compounds aimed at lowering levels of the resulting mutant form of huntingtin.

Optimism around the Roche drug soared after the phase I/II trial showed that tominersen significantly lowered levels of mutant huntingtin in the cerebrospinal fluid, without serious side effects. But following a planned review of the data earlier this year, an independent committee of experts recommended the early termination of the trial, concluding that the drug's potential benefits did not outweigh its risks.



A mutant form of the huntingtin protein accumulates in nerve cells.

REDERIC SADOU, ISM/SPL

On 27 April, during a conference held by the CHDI Foundation – a US HD-research organization – Roche revealed that the trial had been halted because tominersen failed to show higher efficacy than placebo – and, when given more frequently, led to worsened outcomes.

'The saddest possible result'

The phase III tominersen trial tested 2 dosing regimens: 120 milligrams of the drug – the highest safe dose, based on earlier trials – given either every 8 weeks or every 16 weeks.

Roche reported that after 69 weeks, people on the 8-week regimen experienced a more marked decline than did those in the placebo group, with worsened outcomes in areas such as motor function and cognition. Participants in the 16-week treatment group had better outcomes than did those in the 8-week arm, but experienced no overall benefit compared with those given a placebo. Those in the treatment group also showed larger increases in the size of fluid-filled cavities in the brain known as ventricles – a process that typically occurs in those with untreated HD – than did those who received a placebo.

"It's the saddest possible result," says Claudia Testa, a neurologist at Virginia Commonwealth University in Richmond, who has received consulting fees from Wave Life Sciences. "It's clearly the right decision to halt dosing, even though I'm sure that was not the outcome anyone hoped for."

Several factors could have contributed to tominersen's failure, says Sarah Tabrizi, a neurologist at University College London and one of the investigators in the Roche trial. The drug suppresses production of the healthy, as well as the mutant, form of huntingtin, and this could have caused problems. Other possibilities are that the ASO did not reach the right parts of the brain, or that the disease had simply progressed too far for the drug to be beneficial. It will take several months of further analysis to pinpoint what went wrong, Tabrizi adds. Roche's results were preliminary, and important data are still being assessed.

Guarded optimism

Wave Life Sciences' trials were testing ASOs that leave the healthy version of huntingtin intact by targeting small mutations – known as single nucleotide polymorphisms (SNPs) – that occur only in the faulty gene. These occur in a subset of people with HD.

But two such compounds failed to significantly lower levels of mutant huntingtin in early phase I/II trials, leading the firm to abandon their development. The findings from those trials suggest that "we didn't get enough drug where it needed to be to have an effect", says Mike Panzara, the company's chief medical officer. This is a different problem from that seen with tominersen, which did lower levels of the mutant protein but did not seem to slow progression of the disease. Wave does have a third Huntington's ASO in development, which goes after a different SNP and has chemical modifications that improve the drug's potency and ability to reach its targets.

And although hopes for a genetic therapy for Huntington's have been dashed – at least temporarily – researchers are eagerly awaiting the results of a large phase III trial of an ASO for motor neuron disease (amyotrophic lateral sclerosis, or ALS). What happened with tominersen is not a cause for concern for this trial, says Don Cleveland, a neuroscientist at the University of California, San Diego, and a consultant for Ionis Pharmaceuticals in Carlsbad, California, which developed both this drug and tominersen. This is because, unlike in the early trials for tominersen, the phase I/II trial of the ALS drug did show signs of slowing the disease's progression in those with a rapidly advancing form of ALS.

"I think we have reason for guarded optimism," Cleveland says.