Good news from uniQure: gene therapy trial on track, and promising data in animals

The first group of 10 participants have been dosed in uniQure's clinical trial of an HD gene therapy, and three new manuscripts describe safe, widespread huntingtin lowering in animals.

By Dr Leora Fox | April 15, 2021 | Edited by Dr Jeff Carroll

Two recent press releases from uniQure provide welcome good news: the first ever HD gene therapy, known as AMT-130, has been administered via brain surgery to a small set of participants in an early safety trial. At the same time, uniQure has published findings in HD animal models that increase confidence in the drug's ability to lower huntingtin, especially in parts of the brain most affected by HD.

The first gene therapy for HD

Gene therapy is a technique to introduce, replace, or remove genetic material from a person's cells to treat a disease. In the case of Huntington's disease, current gene therapies seek to inactivate the faulty message (RNA) produced by the HD gene, ultimately lowering the amount of huntingtin protein in the brain or body. There are dozens of research laboratories and companies working on different approaches to this, but uniQure's HD gene therapy, AMT-130, is the first to be tested in humans.

Measuring the contents of tiny biological bubbles found in spinal fluid could be a novel way to detect the long-term activity of AMT-130 and other gene therapies.

Image credit: Alexas_Fotos

How can this be true, when huntingtin-lowering ASOs developed by companies like Roche and Wave have already been in the clinic? ASOs are not usually considered to be "gene therapy" because they must be injected at regular intervals, whereas gene therapy is a one-

time delivery. In the case of uniQure's AMT-130, this involves a surgical procedure to deliver the therapy directly into the deep structures of the brain that are most affected by HD.

The human news: a clinical trial on track

On April 5th, uniQure shared that the first group (cohort) of ten US participants in the AMT-130 trial had been successfully dosed. Because this approach is unprecedented, safety was the first priority in this Phase I/II trial, which began recruiting participants in the summer of 2020, after a slight delay due to COVID-19. At first, a single pair of participants had the surgery, and then uniQure waited three months before dosing the next two. After another three months without any extreme or dangerous side effects, the next six were recruited for a full cohort of ten.

In total, six people have received AMT-130, and four underwent an imitation surgery, which is vital for comparing whether the drug is safe. Despite a global pandemic, recruitment was completed ahead of schedule.

Next steps for human studies

There are two major next steps for uniQure. The first is to continue this Phase I/II trial in the United States with sixteen additional patients, of which ten will receive a higher dose of AMT-130, and six will receive imitation surgery. The second is a new study in Europe, in which 15 individuals with HD will all receive the drug, known as an open-label study.

Like all clinical trial participants, these folks with early HD are taking a huge and selfless leap that will ultimately help shape the future of HD gene therapy. After passing through a rigorous screening process, the surgery itself is an 8-10 hour procedure, guided by MRI, involving the insertion of very tiny tubes into six locations deep in the brain. There is frequent follow-up for a year, and then long-term follow-up for five years.

The very nature of gene therapy means that the procedure can't be reversed: AMT-130 creates a permanent change in each brain cell it reaches. In this case, a harmless virus called an AAV introduces a new piece of genetic material that helps the cell to stop cooking up the recipe for huntingtin protein. The hope, of course, is that this one-time treatment could slow the relentless worsening of HD symptoms. Despite the risks, it's encouraging that no major safety issues have been identified yet, and that uniQure is confidently moving forward with a second, open-label study.

The animal news: strong huntingtin-lowering and safety data

Just a few days after the announcement about their ongoing and upcoming clinical trials, uniQure issued a second press release to share positive news about their findings in animal models. There are two separate publications that strengthen the evidence for safe and potent huntingtin-lowering with a one-time surgical approach using a virus, and a third paper that demonstrates a new way to monitor the lasting effects of AMT-130 in the brain. All three were published by scientists at uniQure in collaboration with academic institutions in the Netherlands (where uniQure is based). Here's a summary of each.

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- The first publication details a study that shows good safety and distribution of AMT-130 throughout the brains of small and large animals. Rats and monkeys underwent a surgery to deliver AMT-130 or a placebo directly to the deep brain areas most affected by HD. These experiments, done in animals that do not carry the HD gene, explored the safety of the procedure and the spread of drug through the brain. uniQure found that AMT-130 spread to many different brain structures. The animals were monitored thoroughly for many months after the treatment, and no safety issues appeared during any of the imaging tests, health observations, or tissue examinations.
- A second study describes strong and long-lasting huntingtin-lowering after AMT-130 treatment of HD minipigs. These animals *do* carry the HD gene. In these experiments, which involved similar surgical procedures, the researchers saw strong and lasting reduction of harmful huntingtin protein levels. This was especially true in HD-affected areas that were injected directly with drug, but they also saw widespread huntingtin lowering throughout the brain for up to a year after the surgery. They were also able to make huntingtin measurements by sampling the animals' spinal fluid, an important point because this is a way to detect meaningful changes during current and future clinical trials.
- Finally, a third team investigated a new way to measure the gene therapy's durability and potency. They worked with both monkeys and human cells grown in a dish to measure the release of tiny biological bubbles that circulate in spinal fluid, known as extracellular vesicles. After delivering AMT-130, the researchers used sensitive tests to measure the contents of these bubbles. They found clues that AMT-130 remained active as a genetic therapy for at least 2 years: the vesicles contained evidence that brain cells continued to produce the "antidote" that targets huntingtin. This could be a novel and more subtle way to detect the long-term activity of AMT-130 and other gene therapies.

The take-home message

Taken together, the animal data from uniQure provide evidence that AMT-130 spreads efficiently throughout the brain and can lower huntingtin protein, and this is excellent news for the ongoing and future clinical trials taking place in North America and Europe. Long before this official release, uniQure certainly referred to this positive animal data to help design and plan human studies of AMT-130. It takes time to prepare and submit data for publication in scientific journals, and it's exciting when they finally come out, in this case confirming promising results and spreading awareness of HD research to the wider medical community.

It is worth noting that none of these papers, nor these early clinical trials, explored the effect of AMT-130 on symptoms or behavioral signs of HD. This research, both animal and human, is focused on safety, huntingtin-lowering, and delivery of a novel gene therapy to the brain. AMT-130 may lower huntingtin in animals and so far has not caused major danger to a small group of people, but there's a lot of work to come to test its safety and its ability to help with symptoms or alter the course of HD.

Despite recent disappointing news from Roche and Wave regarding their trials of huntingtin-lowering ASOs, there is still wide consensus within the scientific community that there is therapeutic promise in targeting the genetic cause of Huntington's disease. uniQure's experimental therapy is one of dozens in development that aim to lower levels of huntingtin protein. AMT-130 targets both normal and harmful huntingtin, using a virus to spread the drug throughout the brain. Other companies are focused on lowering harmful huntingtin, and still others are using different messenger systems, modes of delivery, or dosing regimens - testing a major field hypothesis from many angles.

As evidenced by these recent press releases from uniQure (and others!), there is still hope in huntingtin-lowering, as well as many other approaches to HD biology and symptoms. There's a lot of work to be done, including years of careful monitoring of these brave initial participants, but we're encouraged by the positive preclinical findings and the pace at which clinical trials are moving forward.

Dr. Leora Fox works at the Huntington's Disease Society of America, which has relationships and non-disclosure agreements with pharmaceutical companies, including uniQure, Wave Life Sciences, and Roche. Dr. Jeff Carroll has conducted sponsored research with Wave Life Sciences and Ionis Pharmaceuticals on huntingtin lowering. He has no financial interest in any company conducting huntingtin-lowering studies. For more information about our disclosure policy see our FAQ...

GLOSSARY

huntingtin protein The protein produced by the HD gene.

clinical trial Very carefully planned experiments designed to answer specific questions about how a drug affects human beings

placebo A placebo is a dummy medicine containing no active ingredients. The placebo effect is a psychological effect that causes people to feel better even if they’re taking a pill that doesn’t work.

cohort a group of participants in a clinical research study

ASOs A type of gene silencing treatment in which specially designed DNA molecules are used to switch off a gene

magnetic resonance A technique using powerful magnetic fields to produce detailed images of the brain in living humans and animals

AAV a virus that can be used to deliver gene therapy drugs to cells. AAV stands for adeno-associated virus.

RNA the chemical, similar to DNA, that makes up the 'message' molecules that cells use as working copies of genes, when manufacturing proteins.
