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CLINICAL TRIALS

# The endpoint is near

*Better measures of efficacy are needed in trials of treatments for Huntington's disease.*

BY KAT ARNEY

Potential treatments for Huntington's disease are starting to pass through clinical trials, and excitement is building among researchers. "I've been working in Huntington's disease for more than 20 years, and we're in a new era," says Sarah Tabrizi, a clinical neurologist at University College London. "We've previously only had trials looking at drugs that relieve symptoms, but now we know the root cause of the disease, and we're starting to see molecular therapies that target it," she says.

Tabrizi led one such study, which tested whether short pieces of modified DNA known as antisense oligonucleotides (ASOs) could switch off the protein-coding messages transcribed from the gene that is mutated in people with Huntington's disease. The trial received widespread media coverage in December 2017, and researchers, clinicians and patients hope that this gene-silencing approach could provide the first treatment to truly modify the disease (see page S39).

But beneath the positivity lurks a thorny issue for researchers, such as Tabrizi, who are developing treatments. "We absolutely have to be sure they are working," she says. Unfortunately, this is not so easy to determine in Huntington's disease.

Unlike trials of cancer drugs, in which efficacy can be quantified with relative ease — tumours can be seen to shrink, grow or stay the same size — designing trials to demonstrate meaningful improvements in progressive neurological conditions such as Huntington's disease is not straightforward.

The assessment tool used in almost all trials so far is the Unified Huntington's Disease Rating Scale (UHDRS). Developed in 1996 by the Huntington Study Group, an international collaboration, the UHDRS enables doctors to score a person's overall physical and neurological fitness. By testing participants at regular intervals, investigators can work out whether a potential treatment is slowing the progression of the disease, compared with a placebo.

"We've used the UHDRS for many years," says Blair Leavitt, consulting neurologist at the University of British Columbia in Vancouver, Canada. "You can see reliable progression over a certain period, but we need better ways to measure it."

Symptoms such as movement difficulties or cognitive impairment can vary in severity from day to day. This makes it difficult to tell whether a treatment is having an impact on the disease or the patient is just having a good day. And, as Leavitt explains, the subjective nature of functional assessments such as the UHDRS means that they're greatly susceptible to the power of the placebo effect.

The reliability of such tools was thrown into the spotlight with the announcement of results from Pride-HD, a trial of pridopidine (Huntexil) run by Teva Pharmaceutical Industries in Petach Tikva, Israel. Although previous trials of drugs aimed at relieving symptoms were inconclusive, preclinical testing suggested that pridopidine might help to protect neurons from the damaging effects of mutant huntingtin, the toxic protein produced by people with Huntington's disease.

Yet Pride-HD failed to show that pridopidine led to improvements in motor function, which had been declared as the study's primary endpoint (a predetermined milestone that signals the success of a treatment). However, the researchers did notice some improvement in one of the six components of the UHDRS, a measure known as total functional capacity. As one of the most subjective parts of the scale, it considers whether a person is able to work, handle finances or perform self-care tasks.

## PLACEBO EFFECT

The results generated hope that pridopidine might modify the progression of Huntington's disease, as opposed to its symptoms. But, as Leavitt points out, it's more likely that there is an alternative explanation for its effect.

"What's pretty clear to me is that there's a big placebo effect seen with investigator-rated

scales like UHDRS that isn't there in more quantitative measures," he says. "This is why you must define your primary endpoint before the trial — you can't keep going back and looking until you find something that works."

In the absence of better options, and despite its limitations, the UHDRS has been the primary endpoint of choice for two decades. "Objective, quantitative measures will give us more sensitivity," says Leavitt. In 2012, Tabrizi, Leavitt and their collaborators published the results[1] of TRACK-HD — a major study that used a battery of approaches, including brain imaging and cognitive, motor and psychiatric assessments, to monitor more than 100 people with early-stage Huntington's disease over a period of two years. The study also followed carriers of the mutated gene who were yet to show signs of the disease, as well as people without the mutation.

They found a number of measurable features that reflected disease progression, including brain volume on magnetic resonance imaging scans and specific motor and cognitive characteristics. The TRACK-HD team have pooled their data with results from other cohort studies to generate a composite endpoint for future trials. It comprises a suite of cognitive, motor and physiological traits that can accurately assess the progression of Huntington's disease.

Known as the composite UHDRS, it's built on the bones of the original scale and retains the most reliable tests. It also includes further cognitive measures and ditches traits that don't show much progression with time, such as emotional recognition and tongue-muscle strength.

The combined study, which included more than 1,600 people with early-stage Huntington's disease, defined important parameters such as the number of participants that is needed to ensure statistical rigour, as well as the optimal duration of a trial. "Huntington's is a slowly progressive disease, but we showed that we could measure progression in almost everybody over just two years," says Tabrizi.

*"We have exciting new measures and therapies, but we don't have a good way of comparing them."*

The team also reached agreement on the degree to which progression should be slowed for trials of disease-modifying treatments to be deemed a success: people who receive the treatment should show a decline on the composite UHDRS that is 20–30% slower than that of those who receive a placebo.

It seems obvious that trials should be designed to paint the most accurate picture of the benefits and risks of treatments. But Tabrizi suggests that the lack of effective disease-modifying treatments for Huntington's disease, together with the fact that drugs such as ASOs must be administered directly into cerebrospinal fluid (CSF) by lumbar puncture — an uncomfortable procedure in which a needle is inserted into the spinal canal — means that researchers have an ethical duty to make sure that trials are designed as well as possible to reveal whether treatments are working.

## MARKERS OF SUCCESS

Although Leavitt and Tabrizi agree that the composite UHDRS is an improvement on the conventional scale, the hunt is on for biological markers (biomarkers) that change as Huntington's disease progresses. The most obvious candidate is mutant huntingtin, which was thought to leach into CSF from damaged brain cells, in a similar way to CSF biomarkers now used for other neurodegenerative conditions. However, developing a reliable test for quantifying the protein has proved challenging, in part because it is present in CSF at very low concentrations.

As a solution, Leavitt and his colleagues are developing ultrasensitive assays that can detect changes in levels of huntingtin in CSF with disease progression. One approach[2], based on immunoprecipitation and flow cytometry, revealed a decrease in the mutant protein following treatment with ASOs in a mouse model of Huntington's disease, and could serve as a primary endpoint for trials of disease-modifying treatments. An alternative approach[3] that counts single molecules of mutant huntingtin was used in a 2015 trial of ASOs (S39). In any case, monitoring protein levels in CSF would require repeated invasive lumbar punctures.

Other teams are using blood as a more easy-to-access source of potential biomarkers. One such candidate molecule is neurofilament light polypeptide (NF-L) — a component of neurons that is released into CSF as the cells die, eventually making its way into blood. Levels of NF-L in blood plasma mirror those of mutant huntingtin in CSF, and a retrospective study[4] of more than 200 people with Huntington's disease or who carry the mutation that leads to the condition showed that NF-L levels could be used to predict the onset of symptoms, as well as to track disease progression.

Despite promising results, biomarkers in blood or CSF are only surrogates for the underlying disease that ravages the brain. The most direct assay would involve imaging mutant huntingtin in the brain to determine whether it diminishes after treatment, although this is technically challenging. Researchers funded by the US non-profit CHDI Foundation are developing radioactive 'flags', or ligands, that bind to clumps of mutant huntingtin in the brain and can be detected by positron emission tomography. Trials in people are expected to start later this year, according to Cristina Sampaio, chief medical officer at CHDI.

Leavitt and his team are also interested in using wearable sensors to monitor certain biomarkers such as changes in gait or cognitive function in real time. Investigators who use the UHDRS or similar scales can assess the abilities of patients only on the days on which they visit the clinic. However, sensors such as accelerometers can take measurements continually over periods of days, weeks or months, and are even able to monitor sleep patterns and activity levels.

This data stream can be relayed from people's homes to the clinic, creating a more-detailed profile of symptom progression. Initial studies[5] used lab-improvised systems of sensors that are strapped to the chest, wrist and ankles. But off-the-shelf technologies such as fitness trackers or smart watches, in conjunction with smartphones, are likely to become a more practical option. "We can design simple tests on a smartphone to measure gait, walking speed or cognitive function, and we can collect daily data on mood or any other problems they might be having," Leavitt says.

Real-time, remote monitoring of such biomarkers through smartphone apps could reduce the burden of taking part in trials for participants and carers. Travelling long distances to a hospital or trial centre can be arduous, especially for people with advanced Huntington's disease. And the continuous collection of data would make it easier for researchers to follow overall disease-progression trends and to build a more accurate idea of each person's response to treatment.

Despite progress being made, those who are developing new primary endpoints find themselves in a chicken-and-egg situation. To show that they work, trials of disease-modifying treatments need more-appropriate endpoints than those provided by the UHDRS. But the improved endpoints can be validated only against effective drugs, to demonstrate that they accurately measure disease progression and patients' responses to treatment. The current generation of trials is beginning to incorporate measures such as biomarkers and brain imaging as exploratory secondary endpoints, alongside the UHDRS. Despite its flaws, the UHDRS is still the only tried-and-true measure of disease progression available to researchers.

"It's a circular problem. We have exciting new measures and therapies, but we don't have a good way of comparing them to prove that they work," says Leavitt. "Our main clinical endpoint is still the old UHDRS, which isn't that great. We're at the point now where we need an effective therapy to show how things respond."

As Huntington's disease enters an era of targeted molecular treatments, Tabrizi thinks that researchers owe it to those affected to design the best possible trials in which to test such drugs. "We've spent years studying the natural history of the disease to develop our armamentarium for these trials, and we're just waiting for really good drugs," she says. "Huntington's is a terrible disease with a huge unmet need, and patients and their families desperately want treatments that work. We cannot afford to mess this up." ■

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