MedicalXpress

First patients dosed with 'gene silencing' drug for Huntington's disease

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The first few patients have received doses of an experimental RNA-targeting drug for Huntington's disease, it was announced today.

The trial aims to test the safety of an experimental drug known as ISIS-HTTRx, discovered and developed by Isis Pharmaceuticals. Administered by injection into spinal fluid to improve its delivery to the brain, the drug is the first tested in patients that targets the known cause of the disease: a toxic protein called mutant huntingtin which slowly damages and kills neurons, leading to the progressive and ultimately fatal decline in mental and physical abilities that is the devastating hallmark of Huntington's disease.

The huntingtin gene and its lethal protein product have been the focus of intense research across the world since their discovery in 1993. 'Gene silencing' drugs, also known as 'antisense' drugs, are designed to reduce production of a chosen protein by attaching to the mRNA 'message molecule' that's made whenever a gene is activated. ISIS-HTTRx targets the huntingtin message molecule, telling the cell to dispose of it, thereby reducing production of the mutant huntingtin protein.

There are no treatments to prevent, slow or cure Huntington's. RNA-targeting antisense drugs, like ISIS-HTTRx, that lower huntingtin production are widely considered the most promising therapeutic strategy currently under investigation. Isis's Huntington's disease therapeutics underwent over a decade of refinement and preclinical testing before human trials could begin. The first Phase 1/2a trial is

focused principally on safety, using slowly increasing doses of ISIS-HTTRx with careful monitoring of patient wellbeing, scans and laboratory parameters. In addition, the researchers will be looking for chemical signs that the drug is having the desired effect - by measuring the level of mutant huntingtin protein in the cerebrospinal fluid using a newly developed assay.

The trial is set to recruit patients with very early symptoms of Huntington's from six centres in Europe and Canada. Prof Sarah Tabrizi, director of the Huntington's Disease Centre at University College London's Institute of Neurology, is the global chief clinical investigator of the trial. "I'm thrilled that this antisense drug has now been safely administered to the first patients. Families ravaged by Huntington's disease have been waiting for this milestone for decades. I look forward to ensuring the smooth running of this first trial and hopefully seeing ISIS-HTTRx through to efficacy testing and licensing," said Prof Tabrizi.

Isis Pharmaceuticals has partnered with Roche to develop ISIS-HTTRx to treat Huntington's disease. C. Frank Bennett, Ph.D., senior vice president of research at Isis Pharmaceuticals, said,

"Antisense drugs have great potential for many neurodegenerative diseases because they can be tailored to modify the production of any target protein. Huntington's is ideally suited to this innovative therapeutic technology because it comes with genetic certainty: everyone with the mutant gene will get the disease at some point. We designed ISIS-HTTRx to target the huntingtin gene and reduce the production of huntingtin protein, which is the known cause of the disease. This approach has the potential to prevent or slow the progression of this disease. If this first-in-human trial proves the drug is safe, we look forward to continuing our successful partnership with Roche to bring the drug to market."

At UCL, the trial is hosted in the new Leonard Wolfson Experimental Neurology Centre, a custom-built centre designed to accelerate innovative treatments for neurodegenerative diseases, headed by Prof Vincenzo Libri. The administration of the first doses of ISIS-HTT-Rx marks the Centre's first use as a phase 1 'first into human' trial facility, as well as the first time that an experimental drug has been given by spinal injection in the 156-year history of the National Hospital for Neurology and Neurosurgery, part of University College London Hospitals (UCLH) NHS Foundation Trust. Crucial support for this important achievement came from a groundbreaking partnership with the Clinical Trials Pharmacy at nearby Great Ormond Street Hospital (GOSH) where the ISIS-HTT-Rx is prepared for administration. The trial also demonstrates the value of successful collaboration between NHS and academic infrastructures in the form of the National Institute for Health Research (NIHR) UCL/UCLH Biomedical Research Centre.

Cath Stanley, Chief Executive of the Huntington's Disease Association of England and Wales, welcomed the news that the first doses of ISIS-HTTRx had been given to Huntington's patients. "As well as being desperate for good news, the Huntington's community is uniquely well-informed and engaged with progress in research across the world," she said. "RNA-targeting approaches are especially exciting because they tackle the problem at its source - the production of the mutant huntingtin protein. The ISIS-HTTRx trial has been eagerly awaited for many years and we hope that the news from the trial continues to be positive."

Provided by University College London