

EDITORIAL



Oligonucleotide Treatment for Huntington's Disease

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Huntington's disease is a severe autosomal-dominant neurodegenerative disorder that involves chorea, cognitive decline, and psychological problems such as depression, delusions, and impulsive behavior. Nowhere are the manifestations more striking than around Lake Maracaibo in northwestern Venezuela, where the disease is almost epidemic. The Huntington's disease kindreds in Venezuela encompass more than 18,000 persons spanning 10 generations. DNA samples from nearly 4000 patients and family members in this area were used to map the Huntington's gene to chromosome 4 in 1983¹ and to identify the disease gene in 1993.² Subsequent studies in this population have discovered modifiers of age at onset.³ A new prospective treatment specifically targeting the messenger RNA (mRNA) encoding the mutant protein has been tested in patients with Huntington's disease, as now reported in the *Journal* by Tabrizi et al.⁴

Huntington's disease is caused by a trinucleotide repeat expansion that results in an expanded polyglutamine tract in the disease protein, huntingtin. The mutant protein is toxic and prone to aggregation in cell culture, animal models, and human brains. Remarkably, disease manifestations are reversed when the mutant gene is turned off or suppressed in transgenic mice,^{5,6} which suggests that this approach could be effective in humans. Oligonucleotides targeting mutant huntingtin mRNA for degradation did not result in adverse effects when delivered intrathecally in nonhuman primates, and they reduced huntingtin levels throughout the brain.⁶ Although complete loss of normal huntingtin results in embryonic lethality in mice,⁷ partial reduction in levels later in life has an acceptable safety profile. This allows a non-allele-specific

approach, in which the treatment would be suitable for all patients. Importantly, the levels of huntingtin protein can be assessed in the spinal fluid and correlate well with levels in the brain, thus providing a measure of the biologic effect of the treatment.

The trial reported by Tabrizi et al. involved 46 patients who were randomly assigned to receive placebo or one of five doses of the oligonucleotide HTT_{Rx} and followed at nine centers in the United Kingdom, Germany, and Canada. The patients received four injections into the spinal fluid at 4-week intervals, with a 4-month follow-up. The trial agent was not associated with dose-limiting adverse events; the most common adverse effects were related to the lumbar punctures. There was a dose-dependent increase in the concentration of HTT_{Rx} and a decrease in levels of mutant huntingtin protein in the spinal fluid. Remarkably, the reduction in the levels of mutant huntingtin was in a range that is expected to have therapeutic benefit on the basis of studies in animals. This is a pathbreaking trial that strongly supports further development of HTT_{Rx} as a treatment for Huntington's disease. A confirmatory phase 3 trial is now under way (ClinicalTrials.gov number, NCT03761849), with a plan to follow 660 patients worldwide for up to 2 years. Now, 26 years after the discovery of the etiologic gene, a path to modifying Huntington's disease seems clear, with implications for other neurodegenerative diseases that have a known genetic cause. The next step is to determine whether HTT_{Rx} has a clinical effect in a larger number of patients followed over a longer period of time. The current trial was of insufficient size and duration to show a significant difference in clinical measures between patients given the ac-

tive agent and those who received placebo. However, an analysis after the trial showed a correlation of such measures with levels of the mutant protein in the spinal fluid, indicating that reducing the protein level could be beneficial.

The phase 3 trial that has just begun is appropriately designed to determine whether this intervention has a clinically meaningful effect. The ultimate challenge will be to bring safe, effective, and affordable treatment not only to patients in North America and Europe but also to patients with Huntington's disease throughout the world. For those in Venezuela who donated the samples that made this promising approach possible, the treatment should be free.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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1. Gusella JF, Wexler NS, Conneally PM, et al. A polymorphic DNA marker genetically linked to Huntington's disease. *Nature* 1983;306:234-8.
2. The Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell* 1993; 72:971-83.
3. Wexler NS, Lorimer J, Porter J, et al. Venezuelan kindreds reveal that genetic and environmental factors modulate Huntington's disease age of onset. *Proc Natl Acad Sci U S A* 2004; 101:3498-503.
4. Tabrizi SJ, Leavitt BR, Landwehrmeyer GB, et al. Targeting huntingtin expression in patients with Huntington's disease. *N Engl J Med*. DOI: 10.1056/NEJMoa1900907.
5. Yamamoto A, Lucas JJ, Hen R. Reversal of neuropathology and motor dysfunction in a conditional model of Huntington's disease. *Cell* 2000;101:57-66.
6. Kordasiewicz HB, Stanek LM, Wancewicz EV, et al. Sustained therapeutic reversal of Huntington's disease by transient repression of huntingtin synthesis. *Neuron* 2012;74:1031-44.
7. Zeitlin S, Liu JP, Chapman DL, Papaioannou VE, Efstratiadis A. Increased apoptosis and early embryonic lethality in mice nullizygous for the Huntington's disease gene homologue. *Nat Genet* 1995;11:155-63.

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