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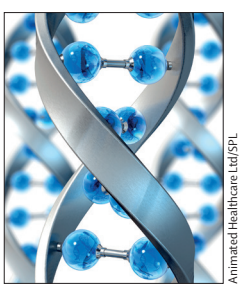
Antisense oligonucleotides might change the therapeutic landscape for Huntington's disease

Huntington's disease is an autosomal dominant neurodegenerative disease that typically presents in midlife with a triad of motor, cognitive, and psychiatric symptoms. Huntington's disease is due to a cytosine-adenine-guanine repeat expansion that results in selective death of the medium spiny neurons in the striatum and associated cortical atrophy. No treatments exist to delay the disease onset and approved treatments are limited to reduction of chorea severity.[1,2]

Hailed by some as the most notable advance since the discovery of the *HTT* gene, Tabrizi and colleagues[3] reported findings of a phase 1–2a trial of the antisense oligonucleotide, HTTRx. The trial randomly assigned 46 patients with early Huntington's disease in a 3:1 ratio to receive either ascending doses (10–120 mg) of HTTRx (n=34) or placebo (n=12) as an intrathecal bolus administration every 4 weeks for four doses. The trial was done at nine centres in the UK, Germany, and Canada and the open-label extension of the administration of 120 mg continues.

Safety, which was the primary endpoint, included physical, neurological, and psychiatric examinations, laboratory assessments, vital signs, electrocardiograms, and neuroimaging sequences as well as open-ended queries about health status. All participants completed the study, and the incidence of adverse events was similar among the groups. Nearly all (98%) participants reported having mild or moderate adverse events. Hospital admission of one patient in the placebo group for headache observation was the only severe adverse event reported. The most commonly reported adverse events were procedural pain and postdural-puncture headache; all resolved spontaneously, and no blood patches were used.

The study was well designed and done rigorously. Dose-dependent decreases in the concentration of mutant huntingtin in CSF were observed. Indeed, this report is the first to suggest that an experimental treatment can lower the presence of mutant huntingtin in CSF with no significant adverse events. Huntingtin might enter the CSF as neurons die and increasing concentrations would therefore reflect more cell death. Although these findings are promising, further work will be needed to replicate these findings.


Animated Healthcare Ltd/SPL

Increases in neurofilament light chain and enlarged ventricular volumes were associated with treatment. Although these changes are not generally considered efficacious, the authors suggest that an inflammatory response to the intervention might underlie the association. Replication of these findings and further longitudinal data both from mutation carriers and patients with the disease will be crucial. As expected, no clinical correlates of treatment effect were identified, since the preclinical phase of Huntington's disease lasts about 35 years.[4,5] Appropriately, a phase 3 trial is being done at 90 worldwide sites in 660 people with early manifest Huntington's disease to investigate the safety and efficacy of an antisense oligonucleotide (NCT03761849). Encouraging news from the American Academy of Neurology meeting showed that open-label extension data from the study by Tabrizi and colleagues[3] could support the phase 3 study, which will compare three treatment groups: a placebo group, a group given an antisense oligonucletoide every 2 months, and another given an antisense oligonucletoide every 4 months. Health-care visits for drug injections three times per year, instead of 12, will substantially improve clinical care guidelines for practitioners and patients, if eventually approved.

Unsurprisingly, Huntington's disease specialty centres report being flooded with individuals requesting to receive the antisense oligonucleotide intervention. Notably, another two antisense oligonucleotide clinical trials in humans are ongoing (allele-specific; NCT03225833 and NCT03225846) and a patent has been granted for single-treatment AAV5 gene therapy planned to begin

in 2019. RNA interference studies using small molecules have also been completed in sheep and non-human primate models of Huntington's disease. Experimental therapeutics in Huntington's disease are approaching a historical peak and outcomes over the next few years will define the therapeutic options available for affected families. Partnership among Huntington's disease volunteers and investigators is crucial to meet the enrolment demands of clinical trials.

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We declare no competing interests.

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Thank you to our peer reviewers in 2018

The Lancet Neurology is proud to be the leading clinical neurology journal, according to the 2018 Journal Citation Report, for another successive year. This achievement is, in great part, due to the clinical and statistical reviewers from around the world who have provided the expert advice to ensure publication of the highest quality articles for our readers. The names of everyone who reviewed papers for the journal throughout 2018 are listed in the appendix; those who reviewed five papers, or more, are marked with an asterisk. We extend our warmest gratitude to all these reviewers.

See Online for appendix

We also recognise that we have a responsibility to our community for equal opportunities. *The Lancet* Group has drawn attention to the evidence that shows women to be vastly under-represented as authors, reviewers, or editorial board members across scientific and medical journals, noting that these inequities are at odds with our values and track record of advocacy.[1] In 2018, around 22% of our reviewers were women. This number falls short in relation to the estimated proportion of around 30% of female neurologists in the USA in 2017, reported by the Association of American Medical Colleges.[2] We aim to facilitate women's participation in peer review and any other of our editorial initiatives.

In this vein, *The Lancet* Group has made a commitment to increase gender equity, diversity, and inclusion in research and publishing, announcing a new Diversity Pledge and a No All-Male Panel Policy.[3] The Diversity Pledge expresses our commitment to increasing the representation of women and colleagues from low-income and middle-income countries among our editors, advisors, peer reviewers, and authors. The No All-Male Panel Policy states that *Lancet* Group editors will not serve as panellists at a public conference or event when there are no women on the panel, and commits us to gender balance on events we organise. *The Lancet Neurology* is committed to these pledges and we hope other journals in our field will follow suit.

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