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Perspective

Perspective: Tominersen Testing Finds a Way Forward

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The winds and the waves are always on the side of the ablest navigators.
-Edward Gibbons

F. Hoffmann-La Roche reported details of its tominersin clinical studies, including the Generation HD1 study designed to delay or improve the course of Huntington's disease, at CHDI's 17th Annual Huntingtons' Disease Therapeutics Conference in March 2022. The failure to achieve clinical success led to the description: "devastating" [1]. I agree that the news was disappointing. Antisense oligonucleotide treatment with the highest tested dose administered intrathecally every other month was associated with ventricular enlargement and worsening of clinical endpoints. Both dosing regimens in the Generation HD1 study significantly lowered mutant huntingtin in the cerebrospinal fluid, but also produced transient increases in cerebrospinal fluid levels of neurofilament light chain, opposite to the expected outcome. What might account for the ineffectiveness of the study and why would F. Hoffmann-La Roche pursue another study?

Let's consider problems with the trial. First, patients with advanced disease were treated. All the patients included in the study had clear evidence of clinical signs and symptoms of disease. It is well known that at clinical presentation many neurons in the neostriatum are lost, estimated at one-half the medium spiny neurons, by far the predominant kind of neuron in the neostriatum. Compare the timing of treatment to interventions in other diseases. Would treatment of type 2 diabetes mellitus be delayed until its complications surfaced – renal failure, vascular disease, retinopathy and neuropathy? Treatment starts when the diagnosis is made, as in high blood glucose or hemoglobin A1c. For Huntington's disease, the risk of disease can be based on genetics. An expanded CAG of 40 or more in the huntingtin gene is associated with clinical disease in middle age, and about 60 or more in adolescence. Single cell RNA seq in neurons in the neostriatum refined our knowledge regarding how CAGs can expand in a given individual [2]. Those HD patients with 40 CAG repeats by genetic testing of blood harbored 60 or more CAG repeats in many neurons post-mortem. The CAG repeat expanded in the brain, predicting more severe disease. Rethinking the diagnosis of Huntington's disease derived from genetics, rather than motor signs alone, is now appropriate.

Second, pathogenesis of Huntington's disease runs through the neostriatum. Information at the meeting imparted that the disease is primarily neuronal rather than glial, although contributions from several cell types could be involved. The implication is that the antisense oligonucleotides need to access neurons in the neostriatum, not an easy task given the deep structure cloaked in the internal capsule and fiber systems. In non-human primates, antisense oligonu-

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cleotide could marginally be detected in the caudate (not significant) and was absent from the putamen [3]. Would the human brain be more accessible? The route of administration through the lumbar space might have impaired distribution to the neostriatum also. Access of RNA oligonucleotides (small interfering RNAs) through the lateral ventricle has demonstrated improved distribution into the neostriatum in non-human primates [4]. Perhaps, target engagement in the neostriatum by antisense oligonucleotides is limited.

Third, because the subjects included in the GenerationHD1 trial may have had the disease process ongoing in the striatum for many years, the neuropil of these study patients was probably disorganized, with many neurons sick and dying, and vasculature disordered. It would be like replacing an aortic valve into a calcified, scarred left ventricle – not the best choice for success. The pathological state of the target tissue dictates treatment before maturity of disease.

All patients sign consent forms. These forms state that the administration of a drug is not a treatment and that patients should not expect beneficial effects. They could experience worsening. Physicians and patients hope that the drug alleviates disease. In the situation for the antisense oligonucleotide, no adverse effects were found in normal non-human primates. If one compares attorneys and scientists, both ask questions. Attorneys ask questions when they know the answer. Scientists ask questions when they do not know the answer to reach truth. Our enthusiasm to achieve therapy sets up patient and physician alike for disappointment.

Why would F. Hoffmann-La Roche start another trial? I asked Drs. Lauren Boak and Peter McColgan of F.Hoffmann-La Roche Ltd and Roche Products Ltd this question. Mining the data unearthed a trend that an adjusted, low dose of antisense oligonucleotide, administered at less frequent intervals might mitigate the neuropathology [4]. Less severely affected patients might tolerate the adjusted protocol. A revised staging of Huntington's disease patients would clarify patient selection [5]. The neurofilament light chain eventually returned to baseline in the initial tominersin studies; this measurement might have a different course with fewer extant, unstable neurons in the second study. Other studies are getting started including AAV-miRNA against huntingtin mRNA [6] and small molecules to target pseudo-exons in huntingtin [7, 8]. I see able navigators catching the winds and the waves.

DISCLOSURES

Neil Aronin, MD, is Professor and Chief of Endocrinology, Diabetes and Metabolism at the University of Massachusetts Chan Medical School. He is a founder of Atalanta Therapeutics and serves on its Scientific Advisory Board. He serves on the Scientific Advisory Board of Biogen in Neurodegenerative Disease. He is an Associate Editor for the *Journal of Huntington's Disease*.

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