Movement Disorders
CLINICAL PRACTICE

IN FOCUS

Antisense Oligonucleotide Therapy for Spinocerebellar Ataxias: Good News for Terrible Diseases

Scoles DR, Meera P, Schneider MD, et al. Antisense oligonucleotide therapy for spinocerebellar ataxia type 2. Nature 2017; 544:362–366.

Spinocerebellar ataxia type 2 (SCA-ATXN2) is an autosomal-dominant disease caused by CAG repeat expansion in the ATXN2 gene that codes for ataxin-2 protein (ATXN2).[1] It is characterized by progressive cerebellar ataxia with peripheral neuropathy and slow saccades, however the phenotype may include parkinsonism, dementia, dystonia, chorea, and neuromuscular syndromes.[1,2] Unfortunately, no effective treatment is currently available.

Recently, a few studies have explored antisense oligonucleotide (ASO) therapy, a technique that involves the use of a nucleotide sequence complementary to a specific mRNA to inhibit its expression and block the transfer of genetic information from the DNA to the protein product. This is usually accomplished by either inducing degradation of mRNA or by physically blocking the translational machinery. Being that anionic oligonucleotides penetrate the blood-brain barrier poorly and (in the case of brain disorders) the delivery of ASO therapies is fairly complex, an intracerebroventricular infusion is typically used.

ASO therapy was applied for SCA-ATXN2 for the first time in a pivotal, breakthrough study by Scoles and colleagues.[3] The ATXN2 does not show repeat-associated non-AUG translation or lethal homozygous gene knock-out in animal models, as seen in other disorders that are linked to CAG repeat expansions.[4] In the study, the first step was the in vitro development of ASOs that were tested in vivo for tolerability, biochemical, and physiological effects. An ASO-designated ASO7 was the most adequate, subsequently tested in various doses to determine which level induced the most significant reduction in ATXN2 without inducing cerebellar glial activation. The next phase was the treatment of ATXN2-Q127 mice, which had a human ATXN2 cDNA transgene with 127 CAG repeats and ASO7 intracerebroventricular injections starting at 8 weeks of age (coinciding with the age of motor phenotype onset). Motor performance was tested at 5, 9, and 13 weeks after the injection. The effect was compared to saline injected mice and the comparison showed significantly improved motor performance of the ASO7-injected animals. To confirm the findings in an additional model, the authors tested the BAC-Q72 with 72 CAG repeats, a model that approximates human disease in terms of clinical manifestations and progression and contains the entire human gene in its proper intronic–exonic context. What remained in the second experiment was methodologically identical to the first mice model, and with similar results. In addition, human ATXN2 was not detected in cerebellar lysates from treated mice by western blotting, however the rotarod performance of the ASO7 treated mice did not perfectly mirror that of wild-type mice, indicating that additional treatment would be necessary to restore cerebellar function. The experiment also demonstrated a similar physiological effect on the firing frequency of Purkinje cells of the ATXN2-Q127 mice.[3]

In conclusion, despite the effort needed to translate such animal model findings into a truly meaningful clinical intervention in humans affected by these disorders, the results are highly encouraging. This report highlights the potential use of ASOs therapy for treatment in a variety of human neurodegenerative diseases due to polyQ-induced molecular dysfunction.[3]

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first, B. Review and Critique.

H.A.G.T.: 3A, 3B
C.H.F.C: 3B
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Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board was not required for this

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Relevant disclosures and conflicts of interest are listed at the end of this article.
Received 28 February 2018; revised 13 April 2018; accepted 16 April 2018.
Published online 25 May 2018 in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/mdc3.12627

work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflicts of Interest: The authors report no sources of funding and no conflicts of interest.

Financial Disclosures for previous 12 months: The authors report no conflicts of interest.

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