Novel Treatments and Clinical Research in Child Neurology

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KEYWORDS

• Child neurology clinical research • Child neurology residency training
• Antisense oligonucleotide • Enzyme replacement • Gene therapy

KEY POINTS

- Research into therapeutics for neurologic disorders in children has markedly increased due to greater molecular understanding of the pathogenic mechanisms of disease.
- Child neurology residency programs should provide trainees with experiences that build interest and skill in clinical research.
- Novel treatments for heretofore untreatable and fatal disorders promise to change the field of Child Neurology.

INTRODUCTION

Child neurology has transformed into a field of novel therapies aimed at the root cause of disease. In this article, the authors cover some of the recent treatments that turned degenerative and fatal disorders into chronic conditions. The future for therapy in child neurology is very bright, and the practicing child neurologist will have to understand the principles of these novel therapies.

The molecular understanding of the pathogenic mechanisms responsible for neurologic diseases of children has led to a remarkable period of research that addresses the root causes of diseases. The promise of this research has been realized with cures and treatments that correct underlying deficiencies. The breakneck rate at which new research is being proposed promises to usher in a transformation of child neurology from a diagnostic and supportive field into an interventional one.

ENZYME REPLACEMENT

Somatic diseases resulting from enzyme deficiencies can be treated with intravenous infusions of enzyme, such that enzyme replacement is relatively common for somatic

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disorders. The brain remains a challenging organ for enzyme replacement because most proteins do not cross the blood-brain barrier.

Therefore, enzyme replacement for brain disease is and will be challenging. Cerliponase alfa, a recombinant tripeptidyl peptidase (actually manufactured as a proenzyme), is the first of the enzyme replacement strategies to have received full approval for a human neurologic disorder, late infantile neuronal ceroid lipofuscinosis (*CLN2*-related Batten disease).[1] In a remarkable achievement, this treatment, inspired by a treatment of a spontaneously occurring Beagle model[2] of late infantile neuronal ceroid lipofuscinosis, is an enzyme replacement given every 2 weeks via a ventricular port in humans. It leads to an arrest of the disorder that is a rapidly progressive neurodegenerative disorder. Because the treatment has only been in existence for about 5 years, it is not known if this will prevent only brain disease and allow disease to progress in the eyes or even other tissues. Because this is an enzyme replacement, reactions are common, as seen in other enzyme replacements. Premedication with diphenhydramine and methylprednisolone is often used. Because enzyme deficiency is often a cause for neurologic disease, this strategy may be used in other disorders.

ANTISENSE OLIGONUCLEOTIDES

Antisense oligonucleotides (ASOs) are small DNA molecules that can modify RNA and protein expression, target mutant allele expression, prevent DNA silencing, and produce dosage effects.[3] The targeting and design of these ASOs is beyond the scope of this chapter and have been the subject of much study. However, the human benefits of these small molecules have been demonstrated in spinal muscular atrophy, muscular dystrophy, and in an N-of-1 study, *CLN7*-related Batten disease.

In spinal muscular atrophy, children lack the ability to make enough survival motor neuron (SMN) protein for their anterior horn cells to survive. This protein can be produced via transcription from *SMN1* and less efficiently from *SMN2*. Nusinersen modifies the transcripts (modifies splicing) from *SMN2* to make the SMN protein more efficiently, thereby preventing disease progression and in some cases improving neurologic function.[4,5]

Duchenne muscular dystrophy results from loss-of-function variants in *Dystrophin*. This gene is long (79 exons), and disease results often from premature stops owing to various mutations. ASOs designed to treat Duchenne have had success by skipping exons in a personal mutation-specific manner, thereby leading to the production of some protein.

Pointing to a possible future for ASOs, a child affected by *CLN7*-related neuronal ceroid lipofuscinosis (*CLN7*-related Batten disease) was found to have a splice-altering intron insertion in one allele of *CLN7* and a pathogenic variant in the other allele. A personalized ASO was designed to alter the transcripts from the intron-inserted variant, thereby enhancing production of an intact *CLN7* transcript.[6] This treatment has been rendered intrathecally via a lumbar puncture every 3 months, similar to that of nusinersen.

Clinical trials for other ASOs to unmask imprinted (silenced) genes in Angelman syndrome, dosage effects from duplication syndromes, and other personalized ASO strategies are underway.

VIRAL VECTORS TO INTRODUCE GENES

Adeno-associated viruses (AAV) to introduce genes into the central nervous system (CNS) has been a strategy for several recent clinical trials, including a transformational one to treat spinal muscular atrophy. The efficiency of these vectors to introduce

genes into neurons has been the subject of much of the criticism of this approach. Although this remains debated, the efficacy of an AAV-9 introduction of *SMN* into the CNS of patients with spinal muscular atrophy has been dramatically established.[7]

Pharmacologic Agents to Modify Signaling Pathways in Disease

At this point, nearly every signaling pathway in humans has been targeted by pharmaceutical companies, and new agents have been brought to treat neurologic disorders based on the disturbed signaling pathways.

For example, the mammalian target of rapamycin (mTOR) has been inhibited in conditions in which it is upregulated. Tuberous sclerosis is one such disorder that results from hemizygous loss of either *TSC1* or *TSC2*, resulting in upregulation of mTOR. In patients with tuberous sclerosis, the treatment with everolimus has been shown to shrink giant cell astrocytomas and angiomyolipomas and to lessen seizure burden.[8–11]

Neurofibromatosis 1 results from loss-of-function mutations in *NF1* that results in upregulation of the Ras–mitogen-activated protein kinase (MAPK) pathway. Selumetinib, a selective MAPK 1 and 2 inhibitor, shrinks inoperable plexiform neuromas in patients with neurofibromatosis type 1.[12]

CLINICAL RESEARCH IN CHILD NEUROLOGY

The few examples of dramatic, innovative treatments for child neurologic disorders point to the possibilities that transformational clinical research in our field will lead to a bright future for our patients. However, who will do this research? Are there enough child neurologists trained for clinical research to provide the throughput necessary to realize this future?

The regulatory components, the care of the vulnerable child in an experimental trial, the time constraints on the practicing child neurologist, and money, all conspire to make the charge of accomplishing the necessary research to transform our field challenging. Yet, we must train the next generation of child neurologists to do clinical research, to understand the basis of new and transformational clinical trials, and we must become an interventional field for our patients.

DISCLOSURE

The authors have nothing to disclose.

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