PPN

Personalized Psychiatry and Neurology

Brief Review

New Hope: Using Gene Therapy to Treat Rare Neurological Diseases

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Citation: Rizvanov, A.A. New Hope: Using Gene Therapy to Treat Rare Neurological Diseases. *Personalized Psychiatry and Neurology* **2023**, *3 (1)*: 3-6. https://doi.org/10.52667/2712-9179-2023-3-1-3-6

Chief Editor: Nikolaj G. Neznanov, D Med Sci, Professor

Received: 03 April 2023
Accepted: 15 April 2023
Published: 15 May 2023

Publisher's Note: V.M. Bekhterev NMRC PN stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract: Gene therapy is a promising treatment approach for rare/orphan neurological diseases that have limited treatment options and no cure. This article provides a brief overview of different types of rare hereditary neurological diseases and discusses existing gene therapy drugs approved for their treatment. Despite challenges associated with the development and implementation of gene therapy, including cost, delivery, and long-term safety and efficacy, the potential benefits of gene therapy make it a compelling area of research for the treatment of rare hereditary neurological diseases.

Keywords: *gene therapy, hereditary neurological diseases, orphan diseases.*

Introduction

Rare hereditary neurological diseases, also known as orphan diseases, encompass a wide range of genetic disorders that primarily affect the nervous system and are often caused by mutations in a single gene. These diseases are considered rare, affecting less than 1 in 2000 people, and can have a profound impact on quality of life. There are over 7000 identified rare hereditary diseases, many of which affect the nervous system, and new ones are discovered each year [1]. However, only a few have effective treatments available. Some common examples of rare hereditary neurological diseases include Huntington's disease, Amyotrophic Lateral Sclerosis (ALS), Spinal Muscular Atrophy (SMA), Metachromatic Leukodystrophy (MLD), and Tay-Sachs disease (TSD) [2-4]. These diseases are often progressive and can have a significant impact on the affected individual and their families, leading to reduced lifespan and substantial morbidity. Symptoms can vary greatly, ranging from motor deficits and cognitive decline to sensory abnormalities and seizures.

Rare hereditary neurological diseases are inherited in an autosomal dominant, autosomal recessive, or X-linked manner, depending on the gene affected and the specific mutation involved. Autosomal dominant disorders are caused by a mutation in one copy of the gene and the affected individual has a 50% chance of passing the mutation on to their offspring. Examples of autosomal dominant disorders include Huntington's disease and Spinocerebellar ataxia (SCA) [5, 6]. Autosomal recessive disorders are caused by mutations in both copies of the gene, and the affected individual must inherit two copies of the mutated gene, one from each parent. Examples of autosomal recessive disorders include SMA and MLD [2, 3]. X-linked disorders are caused by mutations in genes located on the X chromosome and often affect males more severely than females because they have only one copy of the X chromosome. An example of an X-linked neurological disorder is X-linked adrenoleukodystrophy (ALD), which affects the nervous system, specifically the

myelin that surrounds and protects nerve cells in the brain [7]. Some hereditary neurological diseases are multifactorial with poorly understood etiology.

Currently, there is no cure for the majority of rare hereditary neurological diseases, and treatment options are limited. Symptomatic treatment can help manage the symptoms of the disease and improve the patient's quality of life. This may include physical therapy, speech therapy, and medication to manage pain and other symptoms. However, these treatments do not address the underlying genetic cause of the disease and are often not effective in stopping or reversing the disease progression. Therefore, there is a critical need for new and innovative therapies, such as gene therapy, to treat these devastating diseases.

Gene therapy is a promising treatment approach for rare hereditary neurological diseases. It involves the delivery of a functional copy of the mutated gene with the aim of restoring normal gene function or compensating for the loss of gene function due to mutation, or suppressing defective gene to prevent it from causing disease. In addition, gene therapy can directly affect the human genome through the insertion, deletion, or modification (gene editing) of specific genes in a person's genome.

Several preclinical and clinical studies have been conducted for various rare hereditary neurological diseases to evaluate the safety and efficacy of gene therapy. However, there are just few gene therapy drugs approved worldwide to treat hereditary neurological diseases.

Discussion

Spinraza is an FDA-approved medication that was first approved in 2016 for the treatment of spinal muscular atrophy (SMA), a rare genetic disorder caused by a deficiency of the survival motor neuron (SMN) protein. Spinraza is an antisense oligonucleotide that works by increasing the production of functional SMN protein, which is critical for the survival of motor neurons that control muscle movement. It is administered through intrathecal injection directly into the spinal canal, and multiple doses are required over the course of the patient's lifetime. Spinraza has been shown to be effective in improving motor function and extending survival in patients with SMA.

Zolgensma is another gene therapy drug that was approved by FDA in 2019 for the treatment of SMA. Zolgensma is a one-time infusion of a functional copy of the *SMN1* gene, delivered using an adeno-associated virus (AAV) vector, which is designed to replace the defective gene and restore normal gene function. It is considered a promising therapy for SMA, with clinical trials demonstrating significant improvements in motor function and survival in infants treated with Zolgensma.

Libmeldy (cryopreserved autologous CD34+ cells transduced with lentiviral vector containing human *ARSA* gene) - Approved by the European Medicines Agency in 2021 for the treatment of metachromatic leukodystrophy caused by mutations in the *ARSA* gene. Libmeldy is administered as a one-time infusion directly into the cerebral spinal fluid via a catheter placed in the brain.

Other gene therapy drugs for inherited diseases exist, such as Luxturna for the treatment of inherited retinal disease caused by mutations in the *RPE65* gene, or Glybera for the treatment of lipoprotein lipase deficiency caused by mutations in the *LPL* gene. These conditions are not primarily neurological disorders, but they do affect some functions of the nervous system.

Despite the promising results of these studies, there are still many challenges to overcome in the development and implementation of gene therapy for rare hereditary neurological diseases. These challenges include the delivery of the therapy to the appropriate cells and tissues, the potential for immune responses to the viral vectors used for gene delivery, and the long-term safety and efficacy of the therapy.

Cost is a major consideration when it comes to gene therapy drugs for hereditary neurological diseases. These treatments are often very expensive, with prices ranging from hundreds of thousands to millions of dollars per patient. For example, Zolgensma,

one of the most expensive drugs in the world, costs around $2.1 million per treatment. The high cost of gene therapy drugs for hereditary neurological diseases has raised concerns about access to these treatments, as they may not be covered by insurance or government healthcare programs. This has led to debates about how to make these treatments more affordable and accessible to those who need them. In the Russian Federation, certain gene therapy drugs for hereditary neurological diseases may be provided to eligible patients free of charge through the Fund for the Support of Children with Severe Life-threatening and Chronic Diseases, including Rare (orphan) diseases, "Circle of Good", which was established by the Order of the President of the Russian Federation No. 16 of 05.01.2021.

At Kazan Federal University, we are actively engaged in developing gene and gene-cell therapy drugs for the treatment of rare (orphan) hereditary diseases, including ALS, MLD, TSD, and others [3, 4, 8]. Additionally, we are researching the use of gene therapy drugs to stimulate neuroregeneration and provide neuroprotection through expression of various growth factors, which can potentially help patients with neurological diseases and trauma by slowing down disease progression and aiding in recovery after other treatments [9, 10].

Conclusions

In conclusion, rare hereditary neurological diseases are a diverse group of genetic disorders that have a significant impact on the affected individuals and their families. Currently, treatment options are limited, and there is no cure for these devastating diseases. Gene therapy is a promising approach for the treatment of rare hereditary neurological diseases, and there have been promising results in preclinical and clinical studies. However, further research is needed to overcome the challenges and ensure the safety and efficacy of gene therapy for these disorders.

Conflicts of Interest: The author declares no conflict of interest.

Acknowledgments: This paper has been supported by the Kazan Federal University Strategic Academic Leadership Program (PRIORITY-2030).

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