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Advanced therapeutic strategy for hereditary neuromuscular diseases

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https://doi.org/10.1016/j.ymthe.2021.12.004

Two manuscripts published recently in The Lancet Child and Adolescent Health, both address the efficacy of an advanced therapeutic strategy for hereditary neuromuscular diseases. Weiß et al. present real-world evidence of gene replacement therapy in spinal muscular atrophy (SMA).[1] SMA is a hereditary lower motor neuron disease sharing a global incidence of around 1 in 10,000 live births.[2] SMA was first described clinically in the 1890s but the first disease-modifying treatment, the antisense agent nusinersen (Spinraza), was only approved by the FDA in 2016. A single-dose gene therapy for SMA, onasemnogene abeparvovec (Zolgensma), comprising an AAV9-based vector delivery of an *SMN1* transgene, was approved by the FDA in 2019 and is currently the only approved gene therapy for systemic administration in children.[3] Recently, Novartis reported that 1,400 Zolgensma doses had been administered worldwide since marketing authorization. Weiß et al. evaluated the outcome of Zolgensma treatment in 76 children from Germany and Austria. This real-world experience largely confirms the observation from the clinical trials that the motor scores of both naive and previously treated patients improved after Zolgensma treatment. Side effects did occur as expected; six patients developed acute liver dysfunction, including one with acute liver failure. This report enforces our confidence toward the efficacy of Zolgensma, but also reminds us about the potential hazard, particularly in patients who are older and higher in body weight. In addition, reports of thrombotic microangiopathy (TMA, Novartis safety report) have now been added to the Zolgensma label as a boxed warning in the prescribing information. Providers should also be aware that activation of complement leading to TMA can also lead to complement depletion and susceptibility to infection with encapsulated microorganisms, which has been confirmed in the Novartis safety reports. Therefore, careful monitoring of early lab findings, especially at days 4–5 post dosing should be evaluated for signs of TMA and complement activation by measurement of LDH, platelets, d-dimer, and C4.

In a separate article, Ditters et al. present the effect of alglucosidase alpha dosage on survival and walking ability in patients with classic infantile Pompe disease.[4] Pompe disease is a rare hereditary neuromuscular disease first described in 1931. The first treatment for Pompe disease, alglucosidase alpha (Myozyme and Lumizyme) was approved in 2006 and this enzyme replacement therapy (ERT) has been shown to change the natural history of Pompe disease especially following early diagnosis and treatment.[5] Ditters et al. evaluated 124 patients from France, Germany, Italy, and the Netherlands, and demonstrated that survival was significantly greater in the high-dose (40 mg/kg/week) group compared with the labeled-dosage (20 mg/kg/eow) group. This is an important study that will impact treatment guidelines and improve outcome in patients. However, it took 15 years following approval and ongoing investigation by care providers and independent investigators to bring these new findings to light, highlighting the long road toward improved treatment guidelines where an unmet need remains. The road can be particularly long and arduous for rare diseases because of limited clinical observations in conditions with low prevalence.

Challenges remain for these new therapeutic modalities for hereditary neuromuscular diseases. First, muscle represents three-quarters of our body mass and muscle cells uptake the infused enzymes poorly, and therefore dosage of ERT for infantile-onset Pompe disease (40 mg/kg/week) must be much greater than that for other lysosomal storage diseases (LSDs; usually 1 mg/kg/week). Gene therapies for Pompe disease and other muscular diseases are still in early development, and currently only a few oligonucleotide and small-molecule therapies have been approved for a small portion of patients with Duchenne muscular dystrophy.

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Unfortunately, deaths were recently reported from a gene therapy trial for X-linked myotubular myopathy.[6]

Second, many hereditary diseases affect the central nervous system. ERT is suboptimal for preventing neurodegeneration in LSDs, including Pompe disease, because of the failure of the recombinant enzyme to cross the blood-brain barrier (BBB). Intracerebroventricular administration of the enzyme using an implanted cerebrospinal fluid reservoir provides a continuous supply of enzymes to the brain but is difficult to maintain due to adverse reactions, including infection. Modification of the enzymes to enhance BBB penetration is being developed.[7] Systemic gene therapy is being applied clinically as an alternative treatment to ERT. Intraparenchymal administration can be useful when the target area in the brain is localized, as in the case of aromatic L-amino acid decarboxylase deficiency.[8] The European Commission has also granted market authorization for lentiviral vector-modified autologous hematopoietic stem cell transplantation for metachromatic leukodystrophy.

In early onset myopathies, such as Pompe disease, the impact of increased body mass on treatment durability must be considered. Strategies to allow for re-administration of AAV vectors will be required in this context. Also, viral vector-associated complications have also been observed, especially the systemic inflammatory response that can result in severe or life-threatening complications.[1] Another consideration is the possibility of insertional mutagenesis leading to tumorigenicity. Therefore, long-term follow up is recommended.[9] Some of the complications are dose-dependent, which can be more serious in the treatment of muscular diseases because of the requirement of high dosage to distribute to the large muscle mass. Moreover, the understanding of new or unexpected phenotypes after prolonging the lives of patients by such advanced therapeutics is a substantial undertaking, as shown by the study of Ditters et al. in infantile-onset Pompe disease. Therefore, we need to cautiously follow up patients who receive new advanced therapeutics for both complications and unusual symptoms and signs. The community of treating physicians who serve the rare disease community should strive to continually improve the outcomes of patients while carefully evaluating risk-benefit and maximizing safety.

DECLARATION OF INTERESTS

W.-L.H. licenses a gene therapy to PTC therapeutics and receives honoraria and research grants from PTC. S.-I.M. owns equity in Gene Therapy Research Institution, Co., Ltd (GTRI), and receives a research grant from the GTRI. In addition, S.-I.M. is an advisory to PTC therapeutics. He has also received honoraria from PTC therapeutics and Novartis. B.J.B. reports receiving personal fees from Sanofi Genzyme for membership in the Pompe Registry Advisory Board. Y.-H.C. received honoraria from Sanofi Genzyme and Novartis and is a member in the Pompe Registry Advisory Board and also received research grants from Sanofi Genzyme.

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