Editorial

The Importance of Family and Caregiver Perspectives of Emerging Gene Therapies

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In 2017, Mendell et al[1] reported on the outcomes of a single-dose IV adeno-associated vector containing DNA for survival motor neuron 1 (*SMN1*) for the treatment of spinal muscular atrophy type 1 (SMA1), a progressive, fatal motor neuron disease that presents in infancy. This ground-breaking study reported highly promising results for improved neuromuscular outcomes and survival, and it led to the US Food and Drug Administration (FDA) approval in 2019 for onasemnogene abeparvovec-xioi (Zolgensma® [Novartis Gene Therapies, Inc, Bannockburn, IL, USA]). Labeled as the "most expensive drug in the world" with estimated costs exceeding US$2 million per dose,[2] Zolgensma has garnered global debates regarding drug pricing, equitable drug access, and allocation of health resources worldwide. It also highlighted the promise of gene editing therapies for not only improving but also saving lives for a myriad of monogenic gene disorders, eliciting enormous hope for patients and families who are affected by devastating genetic diseases.

By recent reporting, there are >2600 gene editing trials that are ongoing or have recently been completed worldwide.[3] Some have proven highly successful, including the first FDA-approved gene therapy, chimeric antigen receptor T cells targeting CD19 (tisagenlecleucel [Kymriah®, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA]). Tisagenlecleucel has been approved for the treatment of relapsed or refractory pediatric and young adult B-cell acute lymphoblastic leukemia and adult relapsed or refractory diffuse large B-cell lymphoma.[4] Other trials have been halted in light of unanticipated safety concerns, development of new-onset diseases in participating subjects, and/or death. Gene editing trials for the treatment of sickle cell disease and hemophilia have been paused due to subjects developing leukemias and liver carcinoma, respectively.[5] Hope can turn to heartbreak in a blink of an eye.

This month, *Clinical Therapeutics* has chosen to highlight both caregiver knowledge[6] and patient perspectives[7] regarding gene therapies. Each perspective adds valuable insight into the field, which often fails to query front-line individuals about their vantage points of the benefits and potential harm of these emerging therapies. Perhaps no perspective is as enlightening about the long and winding road from gene target to gene therapy to clinical trials to FDA approval as that of the patients and their families. Contributor Erin Ward, Co-Founder and President, MTM-CNM Family Connection, Inc, writes about her personal journey seeking novel therapies for myotubular myopathy, a rare, X-linked neuromuscular disorder affecting an estimated 1:50,000 newborns worldwide.[8] Erin's son, Will, suffered and ultimately died of the disease after 20 years of valiantly fighting, volunteering for clinical trials and advocating for novel therapies to treat this rare disease. Ms Ward writes about the need for complete transparency from pharmaceutical companies throughout drug development. The families who graciously participate in clinical trials must have a clear understanding not only of the risks associated with the treatment and severe adverse events occurring in real time but also their eligibility for obtaining the therapy should FDA approval ultimately be granted. Importantly, there is a strong need for the alignment of treatment goals among families, Pharma, and the FDA. "Success" of a therapy may not be dependent upon a cure but rather be based upon incremental improvements in symptoms that improve daily life functions for affected individuals. These goals directly affect the ability to achieve safe and effective gene dosing that may ultimately not cure a disease entirely but improve the quality of life for many.

Caregivers' understanding of these emerging technologies is also highlighted this month. Hansen et al[6] conducted a survey study of physicians, dietitians, nurse practitioners, and genetic counselors regarding their own understanding of gene therapy, particularly as it related to metabolic disorders. The authors identified a lack of understanding about gene editing and concluded that there is both an "urgent need for education on topics related to gene therapy modalities" and that professional education across the spectrum of caregivers is highly desired.

It is essential that we obtain and understand the perspectives of key stakeholders in parallel to developing new drugs, diagnostics, and therapies. Failing to incorporate the patients' perspectives risks missed opportunities and mistrust; failing to educate the caregivers about emerging therapies results in missed opportunities to heal. True success of any therapy is dependent on a holistic approach to its application that extends beyond safety monitoring and development. Whether it is publishing the results of a clinical trial, reporting on cost-effectiveness analyses, or providing a forum for patients to share their experiences, *Clinical Therapeutics* is proud to provide a voice for all.

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REFERENCES

1. Mendell JR, Al-Zaidy S, Shell R, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. *N Engl J Med*. 2017 Nov 2;377:1713–1722.
2. Nuijten M. Pricing Zolgensma—the world's most expensive drug. *J Mark Access Health Policy*. 2021 Dec 29;10:2022353.
3. Ginn SL, Amaya AK, Alexander IE, et al. Gene therapy clinical trials worldwide to 2017: an update. *J Gene Med*. 2018 May;20:e3015.
4. Braendstrup P, Levine BL, Ruella M. The long road to the first FDA-approved gene therapy: chimeric antigen receptor T cells targeting CD19. *Cytotherapy*. 2020 Feb;22:57–69.
5. https://www.science.org/content/article/gene-therapy-trials-sickle-cell-disease-halted-after-two-patients-develop-cancer?cookieSet=1 (accessed July 24, 2022).
6. Hansen J, Ramachandran R, Vockley J. Survey of health care provider understanding of gene therapy research for inherited metabolic disorders. *Clin Ther*. 2022;44:1046–1056.
7. Ward E. The ultramarathon of gene therapy development for rare diseases: How can we cross the finish line together? *Clin Ther*. 2022;44:1038–1044.
8. https://medlineplus.gov/genetics/condition/x-linked-myotubular-myopathy/#frequency (accessed July 24, 2022).