The Evolution of Sickle Cell Anemia Treatments: From Supportive Care to Gene Therapy

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Introduction

Sickle cell disease (SCD), also called sickle cell anemia, is a severe inherited blood disorder characterized by the production of abnormally shaped hemoglobin, the protein in red blood cells that carries oxygen throughout the body. SCD leads the body to create sticky, stiff red blood cells that can block blood flow when stuck together in small blood vessels; this accumulation causes pain, severe infections, and organ damage (Rees et al., 2010). The genetic illness affects millions worldwide, especially those of African, Mediterranean, and Middle Eastern descent. Over the past century, treatments for SCD have undergone substantial advancements. This article explores a general timeline and notable developments of SCD remedies, detailing notable developments from simple palliative care to recent gene therapies that offer the potential for a cure.

Notable Advancements in the 20th Century

Treatments for sickle cell anemia first aimed to ease acute symptoms and prevent further complications. In the early 20th century, these methods included hydration, pain minimization, and management of infections (Diggs, 1973). This only changed in the 1970s, with the advancement of hydroxyurea, a drug that increases fetal hemoglobin production. The added hemoglobin keeps red blood cells round and flexible, thus decreasing the frequency of sickle cell crises and hospital admissions (Charache et al., 1995). In combating sickle cell disease,

hydroxyurea took the first step towards disease-modifying treatment. The 20th century also witnessed groundbreaking advancements in stem cell research, allowing E. Donnall Thomas to pioneer the first hematopoietic stem cell transplant (HSCT) in 1957. Decades later, in 1984, the first successful case applying HSCT to replace a sickle cell patient's marrow with that of a healthy, compatible donor was reported, displaying the potential for medicine to finally conquer SCD and reverse the disease (Johnson et al., 2020). Unfortunately, that potential failed to become practical , as the treatment was limited by the availability of compatible donors and a high risk of harmful side effects as a result of the transplant (Walters et al., 1996).

Pharmacological Progress in the 21st Century

The 21st century has seen the approval of various treatments that have revolutionized the biomedical industry, including the management of SCD. For one, L-glutamine oral powder (Endari), approved by the FDA in 2017, increases the amount of free glutamine in the blood, which sickle cells can take to generate anti-oxidant molecules. Endari works to neutralize oxidative stress of sickle red blood cells, thus reducing pain crises and acute complications (Niihara et al., 2018). Similarly, drugs such as Voxelotor and Crizanlizumab have recently been approved for public use. Voxelotor increases the affinity of sickle cell patients' hemoglobin for oxygen, thus stabilizing the hemoglobin (Vichinsky et al., 2019). Crizanlizumab is a monoclonal antibody, preventing vaso-occlusive crises in sickle cell patients by inhibiting P-selectin, a cell adhesion protein that plays a key role in mediating inflammation (Ataga et al., 2017).

The most promising treatment of SCD, however, is gene therapy, which addresses the very root of the genetic disease. The most notable gene therapies are gene addition, where a normal hemoglobin gene is inserted in the place of the patient's sickle cell hemoglobin gene, and gene

editing technologies such as CRISPR-Cas9, which directly corrects the sickle cell mutation in the patient's DNA (Hoban et al., 2016). Recently, this theory was applied in Casgevy, the first FDA-approved gene therapy. Casgevy works by making a precise modification in a particular gene, reactivating the production of fetal hemoglobin and helping to dilute the sickle red blood cells characteristic of SCD (Macmillan, 2023).

Conclusion

The progression of sickle cell disease treatment highlights a revolutionary journey from simple symptomatic relief to the promise of a potential cure. Naturally, these advancements reflect broader implications of the scientific and medical communities' progress, with the introductions of personalized medicine and gene therapies. However, challenges remain in the frame of application and mass production, especially with regard to accessibility, affordability, and the long-term impacts and safety of emerging treatments. Collaboration outside the biomedical fields is required to ensure these novel remedies can reach those affected, regardless of social, economic, or geographic status. Meanwhile, scientists will continue to investigate the long-term implications of more recent medical treatments. With sustained effort, the future of sickle cell patients looks to be increasingly bright.

Works Cited

Ataga, K. I., et al. “Crizanlizumab for the prevention of pain crises in sickle cell disease.” *The New England Journal of Medicine*, vol. 376, no. 5, February 2017, pp. 429-439, https://doi.org/10.1056/NEJMoa1611770. Accessed 11 May. 2024.

Charache, S., et al. “Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia.” *The New England Journal of Medicine*, vol. 332, no. 20, May 1995, pp.1317-1322, https://doi.org/10.1056/NEJM199505183322001. Accessed 11 May. 2024.

Diggs, L. W. “Anatomic lesions in sickle cell disease.” *Sickle Cell Disease: Diagnosis, Management, Education, and Research*, Mosby, 1973, pp. 189-229. Accessed 11 May. 2024.

Hoban, M. D., et al. “Correction of the sickle cell disease mutation in human hematopoietic stem/progenitor cells.” *Cell Stem Cell*, vol. 18, no. 5, May 2016, pp. 730-733, https://doi.org/10.1016/j.stem.2016.03.015. Accessed 11 May. 2024.

Johnson, F. L., & Forni, G. L. “Curative therapies: Allogeneic transplantation and gene therapy.” *Sickle Cell Disease and Hematopoietic Stem Cell Transplantation*, Springer, 2020, pp. 117-136.

Macmillan, C. “Casgevy and Lyfgenia: Two Gene Therapies Approved for Sickle Cell Disease.” Yale Medicine, December 2023. Accessed 11 May. 2024. https://www.yalemedicine.org/news/gene-therapies-sickle-cell-disease#:~:text=With%20Casgevy%2C%20an%20edit%20(or,a%20healthy%20hemoglobin%2Dproducing%20gene

Niihara, Y., et al. “A phase 3 trial of L-glutamine in sickle cell disease.” *The New England Journal of Medicine*, vol. 379, no. 3, July 2018, pp. 226-235, https://doi.org/10.1056/NEJMoa1715971. Accessed 11 May. 2024.

Rees, D. C., Williams, T. N., & Gladwin, M. T. “Sickle-cell disease.” *Lancet*, vol. 376, no. 9757, December 2010, pp. 2018-2031, https://doi.org/10.1016/S0140-6736(10)61029-X. Accessed 11 May. 2024.

Vichinsky, E., et al. “A phase 3 randomized trial of voxelotor in sickle cell disease.” *The New England Journal of Medicine*, vol. 381, no. 6, August 2019, pp. 509-519, https://doi.org/10.1056/NEJMoa1903212. Accessed 11 May. 2024.

Walters, M. C., et al. “Bone marrow transplantation for sickle cell disease.” *The New England Journal of Medicine*, vol. 335, no. 6, August 1996, pp. 369-376, https://doi.org/10.1056/NEJM199608083350601. Accessed 11 May. 2024.