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AUTHORS:
CYNTHIA DUAN [1] & VERONICA GRIGANO [1]
[1]Bachelor of Health Sciences (Honours), Class of 2027, McMaster University

ARTIST:
ELAINE WANG [2]
[2]Bachelor of Health Sciences (Honours), Class of 2026, McMaster University

CRITICAL REVIEW

THE APPLICATIONS OF ZYNTEGLO IN TREATING TRANSFUSION DEPENDENT BETA-THALASSEMIA

ABSTRACT

Beta-thalassemia is a hereditary blood disorder, with one of the most severe forms being transfusion-dependent thalassemia (TDT). Zynteglo is a cell-based gene therapy that seeks to provide an alternative for routine blood transfusions required in the treatment of TDT. The manufacturing process of Zynteglo begins with the collection and modification of a patient's hematopoietic stem cells. Functional copies of the beta-globin gene are then introduced to restore normal hemoglobin production. In clinical trials, Zynteglo has demonstrated its effectiveness as a treatment for TDT, with an assessment report led by Northwestern University 78.6% of American patients achieving complete transfusion independence. However, staggering costs, accessibility issues, and safety concerns hinder the acceptance of the drug in major regions of the world. Future considerations must address the risks and barriers associated with the treatment process to foster greater accessibility.

INTRODUCTION

Beta-thalassemia is one of two categories of thalassemia, a group of recessively inherited blood disorders. Thalassemia is characterized by little to no production of hemoglobin, resulting in anemia of varying severity.[1] It occurs as a result of a genetic mutation of the beta-globin gene (HBB), which causes a reduced beta-globin chain availability in the assembly of mature hemoglobin.[1] The most severe form of beta-thalassemia is transfusion-dependent thalassemia (TDT). Also known as beta-thalassemia major, patients with this variation require lifelong routine blood transfusions for survival, starting in infancy or early childhood.[2] Blood transfusions introduce a variety of challenges, including transfusion-associated iron overload, infection, allergic reactions, and hemolytic reactions.[2] In addition, routine blood transfusions are time consuming and inconvenient which can be mentally taxing for many patients and contribute to a decreased quality of life.[3] With 1 in 100,000 individuals estimated to exhibit some form of symptomatic beta-thalassemia, more long-term and sustainable treatments for TDT are required to improve the overall quality of life of patients suffering from this disease.[1]

MECHANISMS OF ACTION

Zynteglo, a cell-based gene therapy, presents a novel approach to the treatment and management of TDT. This treatment aims to help beta-thalassemia patients achieve long-term transfusion independence, potentially eliminating the need for transfusion entirely.[4] The process begins with the collection of autologous blood stem cells, or hematopoietic stem cells (HSCs), from the patient.[5] In the manufacturing phase, Zynteglo is created by using a lentiviral vector (LVV) to incorporate functional copies of a HBB gene, βA-T87Q-globin, into the genome of collected HSCs.[5] The patient then undergoes myeloablative conditioning with busulfan, or chemotherapy, to suppress the immune system and prepare the body to receive the stem cells.[4] The resulting modified autologous stem cells are then reintroduced into the patient's body through intravenous infusion.[5] The stem cells subsequently initiate the production of red blood cells containing active βA-T87Q-globin.[5] This produces normal beta-globin molecule pairs with alpha-globin molecules to form functional hemoglobin and repopulate normal blood.[4,5]

BENEFITS OF ZYNTEGLO

The Phase 1/2 HGB-205 trial enrolled patients with TDT, with the primary goal of the study being the achievement of transfusion independence.[6] Transfusion independence is a critical milestone indicative of Zynteglo's ability to address the underlying genetic defect causing beta-thalassemia. The results from this trial noted a reduction in the frequency of blood transfusions observed in the treated cohort. Most significantly, 78.6% of American patients treated with Zynteglo in the HGB-205 trial achieved complete transfusion independence.[7] The therapy demonstrated its ability to induce sustained production of functional hemoglobin, a clinically meaningful achievement that eliminates transfusion comorbidities such as iron overload.[7]

Two additional Phase 3 studies, HGB-207 and HGB-212, further validated the therapeutic potential of Zynteglo. These investigations aimed to confirm and extend the findings of HGB-205, providing additional data on the efficacy and safety of the treatment through long-term observation of a broader patient population. The results of Phase 3 reinforced the promising outcomes observed in previous trials, with a consistent reduction in transfusion dependence and a sustained improvement in hemoglobin levels. Specifically, 32 out of 36 evaluable patients across HGB-207 and HGB-212 had attained transfusion independence and achieved a normal or near-normal total hemoglobin.[8,9]

Adverse events associated with Zynteglo primarily consisted of patients displaying mild side effects.[10] LVVs with incorporated transgenes can transduce dividing and non-dividing cells, variably insert transgenes into the host genome. This promotes long-term gene expression to correct, introduce or delete DNA sequences. Across all Zynteglo trials, there has been no evidence of insertional oncogenesis, nor any reported instances.[10] Although the risk is still present, the absence of such adverse events in Zynteglo-treated patients provides an additional layer of confidence in the safety of this gene therapy.

The comprehensive and rigorous evaluation of Zynteglo in these clinical trials has not only provided evidence of its efficacy and safety but has also offered insights into the broader impact of the treatment in the lives of TDT patients. The reduction or elimination of the need for regular blood transfusions has profound implications for the overall well-being and quality of life of individuals living with TDT.[3]

CHALLENGES OF ZYNTEGLO

There are several drawbacks of Zynteglo, particularly regarding its accessibility and safety. Zynteglo's market price is incredibly high, ranging from $1.8 million USD in European markets to $2.8 million USD in American markets, which is largely due to the manufacturing company seeking to recoup the high costs of development and drug testing.[11-13] However, this has led to the drug being rejected from European markets after initial approval, as the company failed to negotiate reimbursements within their National Health Systems to cover costs.[13] With Europe being one of the three major continents where TDT is prevalent, this has proven to be a major setback in the usage and accessibility of gene therapy for medicinal purposes.[14]

TDT is also prevalent in the Mediterranean, Middle East, North and Central Africa, and Southeastern and Southern Asia.[14] In fact, these areas are more at risk for TDT compared to the Americas, with only 0-3% beta-thalassemia related gene mutations, in contrast to 0-19% in Europe, 2-18% in the Middle East, 0-12% in Africa, and 0-11% in Southeast Asia.[15] As such, Africa and Asia are two major continents where the feasibility of implementing Zynteglo should be considered.

Although the prevalence of beta-thalassemia is quite high in Africa, the high-cost of a drug like Zynteglo may make for difficult implementation.[14] Instead, they may first prioritize the focus of health infrastructure on more pressing health issues such as tuberculosis, acute respiratory infections, and HIV/AIDS.[17] In addition, the heightened prevalence of beta-thalassemia in Africa does not necessarily predict the incidence of TDT or severity of the disorder.

Zynteglo has not been approved in any Asian countries, which may be due to the differing and lengthy procedures regarding drug approval. For example, it typically takes China an additional five years to approve imported drugs compared to the vast majority of countries around the world.[18]

While Zynteglo has been approved in the United States of America, accessibility concerns remain. The initial high cost of the treatment, along with the limited clinical infrastructure needed to support and monitor the toxic busulfan myeloablative conditioning process, creates several barriers for individuals to access the treatment.[12] As such, the accessibility of Zynteglo and the feasibility of its implementation in various regions becomes an issue.

The safety of Zynteglo has also been an area of concern due to the lack of long-term follow-up after clinical trials, small sample size, and adverse reactions. Typically, long-term follow-up consists of observing participants after 15 years of the initial study. However, due to Zynteglo's novelty, there is no follow-up data of this magnitude, leading to multiple concerns being raised over potential side effects and whether patients will continue to remain transfusion-independent.[10]

A small portion of patients across all Zynteglo trials experienced

adverse events while undergoing treatment including neutropenia, thrombocytopenia, leukopenia, anemia, and lymphopenia, with over 50% of all adverse reactions occurring at a high degree of severity.[19] Furthermore, within the most recent follow-up for two clinical trials, 37% of patients exhibited severe adverse events, with the most common symptoms being pyrexia, thrombocytopenia, liver veno-occlusive disease, febrile neutropenia, neutropenia, and stomatitis.[19] Symptoms of mild severity can be treated with antibodies, corticosteroids, and other minimally invasive administrations.[19,20] However, severe symptoms typically require intravenous solutions and potential hospitalization.[19,20] While some of these issues may be a result of the busulfan myeloablative conditioning rather than the actual drug, this step is still essential for the administration of Zynteglo. As a result, safety concerns for the overall procedure remain. The small sample size of the studies also creates uncertainty when evaluating patient outcomes. Thus, the accessibility and safety concerns that arise from Zynteglo prove that the viability of the treatment is still uncertain.

NEXT STEPS

While Zynteglo has immense potential, it also has several drawbacks that still need to be addressed to improve the viability of the drug. One potential inclusion would be to minimize the immune risk associated with receiving Zynteglo, particularly during the busulfan myeloablative conditioning process. Busulfan myeloablative conditioning can lead to the following adverse side effects: hepatic veno-occlusive disease, interstitial pulmonary fibrosis, seizures, hyperpigmentation, emesis, wasting syndrome, thrombocytopenia, and medullary aplasia.[21] As such, further research on this step is essential to improving Zynteglo's safety profile.

However, it is important to note that Zynteglo is one of several gene therapies that have the potential to target TDT. For example, CASGEVY, a non-viral, ex vivo CRISPR-Cas9 gene edited cell therapy, recently received approval from the Medicines and Healthcare Products Regulatory Agency in the United Kingdom.[22] Similar to Zynteglo, the treatment process involves the removal of autologous stem cells from the bone marrow. However, they are then genetically altered in a laboratory using CRISPR technology and returned to the patient.[23] Currently, the treatment is awaiting further approval from the National Institute for Health and Care Excellence, with the decision likely to be finalized in April or May of 2024.[22]

CONCLUSION

Zynteglo has demonstrated promise across Phase 1/2 and Phase 3 clinical trials by reducing TDT patients' dependence on blood transfusions. However, additional considerations still need to be taken to increase the overall accessibility of the drug and improve the safety profile in both short and long-term settings. Moreover, Zynteglo has become a model of what the future of gene therapy might hold, inspiring future treatments for TDT, such as CASGEVY, and hopefully improving the livelihoods of many patients to come.

REVIEWED BY: DR. JACK GAULDIE (CM, PhD, DSC, FRSC) & DR. MADELEINE VERHOVSEK (MD, FRCPC)

Dr. Jack Gauldie is a Professor Emeritus in the Department of Pathology & Molecular Medicine and the former Vice President of research at St. Joseph's Hamilton. He has completed extensive research focusing on molecular manipulation for the treatment of many diseases including cancer, chronic lung disease, and arthritis.

Dr. Madeleine Verhovsek is the Chief of Medicine at St. Joseph's Healthcare, with a specialty in hematology. She is also an Associate Professor in the Departments of Medicine and Pathology & Molecular Medicine at McMaster University.

1. Galanello R, Origa R. Beta-thalassemia. *Orphanet J Rare Dis*. 2010;5(1):11. Available from: doi:10.1186/1750-1172-5-11.
2. Udeze C, Maruszczyk K, Atter M, Lopez A. PB2339: Projected lifetime economic burden of transfusion dependent beta-thalassemia in the United States. *Hemasphere*. 2022;6(Suppl):2208-2209. Available from: doi:10.1097/01.HS9.0000852180.45597.87.
3. Wangi K, Birriel B, Smith C. Psychosocial burden in transfusion dependent beta-thalassemia patients and its impact on the quality of life and the problem of dignity. *J Taibah Univ Med Sci*. 2023;18(6):1217-1219. Available from: doi:10.1016/j.jtumed.2023.05.002.
4. Asghar AA, Khabir Y, Hashmi MR. Zynteglo: Betibeglogene autotemcel - an innovative therapy for ß-thalassemia patients. *Ann Med Surg (Lond)*. 2022;82:104624. Available from: doi:10.1016/j.amsu.2022.104624.
5. ZYNTEGLOTM (betibeglogene autotemcel). Mechanism of Action [Internet]. 2023. Available from: https://www.zynteglohcp.com/mechanism-of-action [cited 2023 Dec 24].
6. Thompson AA, Walters MC, Kwiatkowski J, et al. Gene therapy in patients with transfusion-dependent ß-Thalassemia. *N Engl J Med*. 2018;378(16):1479-1493. Available from: doi:10.1056/NEJMoa1705342.
7. Committee for Medicinal Products for Human Use. Assessment Report: Zynteglo [Internet]. 2019 April 26. Available from: https://www.ema.europa.eu/en/documents/assessment-report/zynteglo-epar-public-assessment-report_en.pdf [cited 2023 Dec 25].
8. Schneiderman J, Thompson AA, Walters MC, et al. Interim results from the phase 3 Hgb-207 (Northstar-2) and Hgb-212 (Northstar-3) studies of betibeglogene autotemcel gene therapy (LentiGlobin) for the treatment of transfusion-dependent ß-Thalassemia. *Biology of Blood and Marrow Transplantation*. 2020;26(3, Supplement):S87-S88. Available from: doi:10.1016/j.bbmt.2019.12.588.
9. ZYNTEGLO. Zynteglo: Betibeglogene autotemcel. [Internet] 2023. Available from: https://www.zynteglo.com [cited 2023 Dec 23].
10. Zynteglo (betibeglogne autotemcel). Wellmark [Internet]. 2023. Available from: https://www.wellmark.com/-/media/sites/public/files/provider/pharmacy/zynteglo.pdf?sc_lang=en&hash=03F70086EE707467DAB617DD845DE3E6 [cited 2023 Dec 23].
11. Philippidis A. After sparring with payers on pricing, bluebird flies out of Europe. *Hum Gene Ther*. 2021;32(17-18):868-871. Available from: doi:10.1089/hum.2021.29172.bfs.
12. Sheridan C. For hemophilia and thalassemia, a new era of "one-and-done" gene therapies has arrived. *Nat Biotechnol*. 2022;40(11):1531-1533. Available from: doi:10.1038/s41587-022-01555-0.
13. De Luca M, Cossu G. Cost and availability of novel cell and gene therapies. *EMBO reports*. 2023;24(2):e56661. Available from: doi:10.15252/embr.202256661.
14. Origa R. ß-Thalassemia. *Genet Med*. 2017;19(6):609-619. Available from: doi:10.1038/gim.2016.173.
15. Šmith, Yolanda. Thalassemia Prevalence. [Internet] 2022 Aug 30. Available from: https://www.news-medical.net/health/Thalassemia-Prevalence.aspx [cited 2023 Dec 24].
16. Oleribe OO, Momoh J, Uzochukwu BS, et al. Identifying key challenges facing healthcare systems in Africa and potential solutions. *IJGM*. 2019;12:395-403. Available from: doi:10.2147/IJGM.S223882.
17. Boutayeb A. The impact of infectious diseases on the development of Africa. In: Preedy VR, Watson RR, eds. Handbook of Disease Burdens and Quality of Life Measures. Springer; 2010:1171-1188. Available from: doi:10.1007/978-0-387-78665-0_66.
18. Su L, Liu S, Li G, et al. Trends and characteristics of new drug approvals in China, 2011–2021. *Ther Innov Regul Sci*. 2023;57(2):343-351. Available from: doi:10.1007/s43441-022-00472-3.
19. Food and Drug Administration. ZYNTEGLO (betibeglogene autotemcel) suspension for intravenous infusion [Internet]. 2022. Available from: https://www.fda.gov/media/160991/download [cited 2023 Dec 25].
20. Common Terminology Criteria for Adverse Events (CTCAE). Published online 2017.
21. Patel R, Tadi P. Busulfan. StatPearls. 2022 [Internet]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK555986/ [cited 2024 March 3].
22. Kmietowicz Z. Thalassaemia: NHS to offer stem cell transplants to adults who need transfusions. *BMJ*. 2023;383:p2837. Available from: doi:10.1136/bmj.p2837.
23. Wilkinson E. UK regulator approves "groundbreaking" gene treatment for sickle cell and ß-thalassaemia. *BMJ*. 2023;383:2706. Available from: doi:10.1136/bmj.p2706.