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Gene Therapy Treatment for Sickle Cell Disease: Casgevy

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Abstract:

Sickle cell disease (SCD) presents a notable burden on global health, necessitating innovative approaches beyond traditional biomedical paradigms. While existing treatments aim to alleviate symptoms, recent advancements in gene therapy, exemplified by CASGEVY (Exagamglogene Autotemcel), offer transformative potential. CASGEVY, Introducing the maiden FDA-approved gene therapy employing CRISPR/Cas9 technology, targets recurrent vaso-occlusive crises by enhancing fetal hemoglobin (HbF) production. This ex vivo therapy involves precise genome editing of hematopoietic stem cells, promising enduring benefits by reactivating HbF expression. Despite its groundbreaking nature, CASGEVY warrants thorough consideration of administration protocols and potential side effects, emphasizing the need for comprehensive patient evaluation and monitoring.

Keywords – casgevy, exagamglogene autotemcel, gene therapy, sickle cell, CRISPR, progenitor cells, BCL11A gene.

1. Introduction

Sickle cell disease, a hereditary single-gene disorder, stands as a prominent contributor to global rates of mortality and morbidity.[1]Most of the studies conducted on sickle cell disease (SCD) originate from the biomedical fields, predominantly focusing on pathology, genetics, and hematology. However, there is a notable absence of a comprehensive, interconnected, and evolving approach within SCD research, which embraces the broader health systems perspective. The primary aim of a health system, as authored by The World Health Organization (WHO)is to enhance health outcomes and equity in a manner that is responsive, financially equitable, and optimizes resource utilization. This definition encompasses all entities, individuals, and endeavours primarily dedicated to promoting, restoring, or preserving health. [2-3]

A mutation occurring in the β-globin gene result in sickle cell disease (SCD), an inherited condition marked by the synthesis of aberrant hemoglobin, famously termed hemoglobin S (HbS). When deoxygenated, HbS endure polymerization, causing red blood cells (RBCs) to become rigid and fragile, resulting in their sickling. These distorted RBCs are believed to cause recurrent painful vaso-occlusive crises and persistent anemia. Despite the well-documented molecular abnormalities underlying the disease, individuals with SCD may experience various acute and chronic complications affecting multiple organs, such as the kidneys, brain, skin, bones, eyes, lungs, and heart. It's crucial to recognize that the clinical manifestations of this genetic condition can vary significantly among individuals. [4]

Treatment methods for sickle cell disease (SCD), such as blood transfusions, preventive medications like pneumococcal vaccination and penicillin prophylaxis, and hydroxyurea therapy, primarily aim to alleviate symptoms and mitigate the impact of the condition. Without concurrent administration of robust chelation therapy alongside blood transfusions, iron overload may occur due to the inability of transfusions to fully correct the phenotype. While there is substantial evidence supporting the safety of hydroxyurea medication, patient tolerance can vary, and concerns persist regarding its long-term usage. Encouraging the production of fetal globin (HbF, $\alpha 2\gamma 2$), which competes with sickle globin, has shown promise in reducing the symptoms associated with SCD.[5]

2. FDA Grants Historic Approval for Groundbreaking Gene Therapies Targeting Sickle Cell Disease

The U.S. Food and Drug Administration (FDA) has granted approval to CASGEVY (Exagamglogene Autotemcel), marking a significant milestone as the first CRISPR/Cas9-based gene therapy authorized in addressing sickle cell disease (SCD), a distinctive

therapeutic approach emerges. Developed by Vertex and CRISPROT Therapeutics, CASGEVY targets individuals aged 12 and above experiencing recurrent vaso-occlusive crises associated with SCD. This groundbreaking therapy involves the modification of hematopoietic stem cells using precise CRISPR/Cas9 genome editing techniques, leading to increased production of type of hemoglobin found in fetuses (HbF)and mitigating the symptoms of SCD. The significance of CASGEVY's FDA approval, its mechanism of action, and potential therapeutic benefits, underscoring its transformative impact on SCD management.CRISPR/Cas9 technology allows precise DNA manipulation by targeting specific regions for cutting, thereby facilitating accurate editing such as removal, addition, or replacement of genetic material. Following modification, the blood stem cells are reintroduced into the patient's system, where they engraft into the bone marrow and proliferate. This process leads to heightened production of fetal hemoglobin (HbF), a variant known for its role in enhancing oxygen transport. In people with sickle cell disease, increased HbF levels effectively prevent the abnormal sickling of red blood cells.[(6)]

3. Casgevy

Sickle cell disease have emerged as leading examples of CRISPR-based therapeutic genome editing in human diseases. This is highlighted by the landmark regulatory approvals for Casgevy (also known as exagamglogene autotemcel), marking a significant milestone in the field. These therapies involve the modification of the patient's hematopoietic stem cells using CRISPR-Cas9 technology outside the body (ex vivo). Subsequently, these modified cells are re-implanted into thepatient through a single-dose infusion. Prior to in the treatment process, the patient's own stem cells are collected and then exposed to intense chemotherapy to prepare the body for further treatment.. Following this, the modified stem cells are transplanted into the patient, where they become established within the bone marrow. [(7-8)]On November 16, 2023, the UK Medicines and Healthcare products Regulatory Agency (MHRA) granted approval for the use of the genome editing technology, Casgevy (also known as exagamglogene autotemcel). This approval was specifically for the treatment of patients aged 12 years and older who have transfusion-dependent beta-thalassemia and are suitable candidates for hematopoietic stem cell transplantation, but lack a compatible related stem cell donor.[(8-9)]

Additionally, on the same date, Casgevy has been authorized by the MHRA for managing sickle cell disease in individuals aged 12 years and above who encounter repeated vaso-occlusive crises. These patients are also eligible for hematopoietic stem cell transplantation, but do not have an HLA-matched related donor available. [(9)]

4. General description: [10]

Table 1: General description about casgevy

Property	**Description**
Product Name	Casgevy
Active Ingredient	Exagamglogene autotemcel
Composition	CRISPR/Cas9-edited autologous CD34+ cell-enriched population comprising hematopoietic stem and progenitor cells (HSPCs) obtained through genetic modification.
Targeted Gene	The enhancer region specific to erythroid cells within the BCL11A gene.

5. Administration: [11]

Casgevy is customized for every patient. As part of the treatment, the medical professional will administer additional medications, such as a conditioning medication.

The Casgevy therapy consists of 4 key phases.

- **Step1:** The patient will receive a mobilization medication before the treatment. This medication introduces blood stem cells into the bloodstream cells sourced from the patient's bone marrow. After that, the blood stem cells are gathered in a device known as an apheresis machine, which divides the various blood cells. There could be multiple instances of this complete process. It can take up to a week each time.

  "Rescue cells" are additionally collected and retained at the hospital during this stage. The blood stem cells are the patient's own and are retained without treatment as a precaution in the event of any complications during the treatment process. These rescue cells will be returned to the patient if Casgevy cannot be administered following the conditioning medication or if the altered blood stem cells fail to engraft (take root) in the body. The patient will not benefit therapeutically from Casgevy if rescue cells are administered.
- **Step2:** Blood stem cells are harvested and then sent to the production facility to be used in the creation of Casgevy. Before being returned to the healthcare practitioner, it couldTo commence manufacturing and testing, up to six months may transpire from the moment the cells are harvested.
- **Step 3:** The medical professional will administer a conditioning medication for a few days in the hospital, just before to the stem cell transplant. Through the extraction of cells

from the bone marrowthey can then be substituted with the modified cells in Casgevy, this will get the patient ready for therapy. Following this medication, blood cell counts will drastically decline. During this phase and until the Casgevy infusion, the patient will stay in the hospital.

- **Step 4:** During a brief period of time, one or more vials of Casgevy will be infused intravenously into a vein. The patient will remain in the hospital following the infusion so that the medical professional may properly monitor their recuperation. Times may vary, but this can take four to six weeks.

6. Clinical pharmacology[12]

6.1 Mechanism of action:

During early life, the expression of fetal hemoglobin (HbF) gradually declines, typically stabilizing at levels of 2% or lower in most individuals. However, some people exhibit a hereditary persistence of fetal hemoglobin (HPFH) is a condition marked by abnormally elevated levels of HbF that endure beyond childhood. Individuals with both HPFH and sickle cell disease (SCD) often experience fewer complications associated with SCD or even a complete absence of them. Exa-cel aims to mimic this effect by reactivating HbF expression to levels comparable to those seen in individuals with SCD who also inherit HPFH (i.e., greater than 20%).

The applicant envisions a lasting impact from the genetic modifications brought about by exa-cel. This innovative treatment entails the utilization of a ribonucleoprotein (RNP) complex comprising Cas9 and a specifically engineered guide RNA called SPY101. This complex zeroes in on the binding site of the GATA1 transcription factor within the non-coding enhancer region of the BCL11A gene on chromosome 2. Here, the CRISPR endonuclease within the complex triggers double-strand DNA breaks. Subsequent repair of these breaks by nonhomologous end joining leads to alterations in the DNA sequence, disrupting GATA1 binding and diminishing BCL11A transcription in red blood cells (RBCs). This downregulation of BCL11A prompts an elevation in γ-globin production, consequently reducing the presence of βS- globin. It is anticipated that RBCs post-exa-cel treatment will harbour approximately 30% to 50% HbF, potentially offering therapeutic advantages.

6.2 Pharmacodynamics:

Table 2: Pharmacodynamics of casgevy

Parameter	Description

Proportion of alleles with genetic modification	Mean proportion sustained a minimum of 70% consistency from Month 2 onward throughout the entirety of the research period. (Studies 121 and 131)
Total HbF (%) composition	Mean (SD) proportion were at 36.9% (±9.0%) by Month 3 and remained at or above 40% from Month 6 onward.
Correlative Analysis	Demonstrated the relationship between earlier timepoints (e.g., Month 6) and subsequent timepoints (such as Month 12 & 24) regarding parameters such as HbF% and allelic editing in both bone marrow and peripheral blood, highlighting correlation.
Population Pharmacodynamic Model	The empirical model accurately depicted the HbF% versus time trend up to Month 24 with minimal plagiarism.
Dose-Response Relationship	The available clinical data suggests a lack of significant correlation between the dosage of exa-cel and both the levels of HbF% and the clinical efficacy as indicated by VF12 scores
Factors Exploration	No clinically relevant effects observed for HbF% concerning intrinsic, extrinsic, or manufacturing factors
Allelic Editing and γ-Globin Expression	Gene-edited cell persistence correlates with in vivo duration, yet no established threshold links this persistence to levels of HbF (%) or VF12.
Recommended Minimum Dose	A single IV dose of 3.0 × 10^6 CD34+ cells/kg of exa-cel for treating SCD was considered appropriate.
Further Details	Refer to Clinical Pharmacology review memorandum for comprehensive information

6.3Pharmacokinetics

Due to its autologous cellular nature involving ex vivo editing of CD34+ cells, CASGEVY doesn't adhere to traditional research assessing pharmacokinetics, absorption, distribution, metabolism, and elimination.

7. Possible side effects: [13]

Serious side effects may occur shortly after treatment or manifest later on. These include:

- Pain in the upper right abdomen,symptoms like yellowing skin or eyes, unexplained weight gain, limb or abdominal swelling, and breathing difficulties may signal veno-occlusive disease, a serious liver ailment.
- Symptoms like severe headaches, unusual bruising, and prolonged bleeding, or bleeding from various sources like nose, gums, urine, stool, or vomit, could signal thrombocytopenia—a drop in platelet count affecting blood clotting.
- Presence of fever, chills, or infections, which could signal neutropenia, a deficiency in white blood cells known as neutrophils responsible for combating infections.

8. What advantages have studies revealed regarding the efficacy of Casgevy?[14]

The efficacy of Casgevy has been demonstrated through interim findings from two ongoing studies, without comparison to any alternative medication or placebo. In one study involving thalassaemia patients aged 12 to 35, where Casgevy was administered following conditioning chemotherapy, 39 out of 42 patients-maintained haemoglobin levels above 9 g/dL for a minimum of 12 consecutive months without requiring blood transfusions. Additionally, in another study with severe sickle cell disease patients aged 12 to 35, Casgevy proved effective in preventing painful sickle cell crises, with 28 out of 29 patients experiencing no crises for at least 12 consecutive months post-treatment. Notably, none of the patients in this study required hospitalization for painful crises over the same duration.

9. What are the potential hazards linked with Casgevy?[14]

Consult the package leaflet for a comprehensive inventory of potential side effects and usage limitations associated with Casgevy. Predominantly reported side effects linked with Casgevy, affecting over one in ten individuals, encompass headaches, nausea, and muscle as well as bone discomfort. Prior to administering Casgevy, physicians are advised to assess the feasibility of providing patients with necessary pre-treatments.

10. Conclusion

The approval of CASGEVY heralds a new era in SCD treatment, leveraging cutting-edge gene editing technology to address the underlying pathology. By targeting the erythroid-specific enhancer region of the BCL11A gene, CASGEVY aims to sustainably elevate HbF levels, offering potential relief from recurrent crises. However, the implementation of this therapy requires meticulous attention to administration procedures and vigilance for possible adverse events. Continued research and clinical surveillance are imperative to maximize the therapeutic benefits of CASGEVY while ensuring patient safety and well-being in the pursuit of effective SCD management strategies.

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