Review

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Revolutionary breakthrough: FDA approves CASGEVY, the first CRISPR/Cas9 gene therapy for sickle cell disease

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Abstract

Sickle cell disease (SCD) is a hereditary hemoglobinopathy resulting from a β-globin chain mutation that causes abnormal hemoglobin (HbS) polymerization and leads to severe complications. Current treatment options primarily focus on symptom management, with limited curative potential. Recently, Casgevy, the first CRISPR/Cas9-based gene therapy for SCD, has received breakthrough FDA approval. Clinical trials have shown that Casgevy administered to patients aged older than or equal to 12 years enables precise modifications in hematopoietic stem cells, resulting in elevated fetal hemoglobin (HbF) levels and a significant reduction in vaso-occlusive events. Unlike conventional treatments, this therapy offers a curative approach and eliminates the need for recurrent transfusions and transplants, thereby improving the quality of life of patients with SCD. Casgevy has emerged as a beacon of hope for SCD patients and signifies a potential paradigm shift in SCD management due to its safety, curative potential, and transformative impact, positioning it as a groundbreaking intervention. Nevertheless, ethical considerations surrounding CRISPR technology and regulatory frameworks must be addressed to ensure responsible application and equitable access to this one-time gene editing therapy. As the authors celebrate this scientific advancement, sustained interdisciplinary collaboration and ethical scrutiny are essential to navigating the evolving landscape of CRISPR technology in medicine. This review aims to provide a detailed insight into the application of Casgevy, challenges associated with its application, future prospects of this therapy, and its comparison with existing treatment options for SCD.

Keywords: Casgevy, CRISPR/Cas9 therapy, current treatment limitations, ethical challenges, genetic therapy, hemoglobin, sickle cell disease

Introduction

Sickle cell disease (SCD) is one of the most common severe monogenic disorders in the world characterized by intermittent vaso-occlusive events and chronic hemolytic anemia[1]. Although ~100 000 individuals in the USA are affected by SCD, the majority reside in Africa, constituting an estimated total of over 3 million cases worldwide[2,3]. The current treatment options mainly involve supportive care therapies and disease-modifying therapies. Given the well-characterized monogenetic defect underlying SCD since its identification, SCD presents a promising candidate for gene-modifying or replacement therapies. The article provides an overview of current treatment options with a focus on Casgevy, a recent FDA-approved gene therapy, exploring its mechanism of action, implications, future prospects, and potential ethical considerations in the management of SCD. It aims to provide valuable insights into this treatment option, helping people better understand the potential benefits of Casgevy in managing this prevalent inherited disorder.

HIGHLIGHTS

- Casgevy, the first FDA-approved CRISPR/Cas9 gene therapy for sickle cell disease (SCD), offers a curative approach and eliminates the need for recurrent transfusions and transplants, thereby significantly enhancing the quality of life of individuals with SCD.
- Precise modifications via Casgevy elevate fetal hemoglobin levels and reduce the risk of vaso-occlusive events.
- Safety concerns about Casgevy, including mosaicism and off-target effects, necessitate an in-depth exploration of the overall safety profile of the therapy.
- Comprehensive ethical and legal regulatory frameworks are imperative to address societal equity and distributive justice, particularly in light of the substantial costs associated with its implementation.

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Review

Understanding sickle cell disease

SCD is a severe hereditary hemoglobinopathy resulting from a single mutation in the sixth codon of the β-globin chain, causing the substitution of glutamic acid with valine in the adult hemoglobin (Hb) structure[4]. This genetic alteration gives rise to hemoglobin S (HbS), which exhibits a propensity for polymerization, particularly under conditions of reduced oxygen availability. The resultant polymerized sickle hemoglobin (HbS, α2βS2) disrupts the typical biconcave morphology and flexibility of red blood cells, leading to the formation of crescent-shaped cells with increased adhesion to the vascular endothelium. These modified cells can obstruct blood vessels, leading to various complications, including chronic anemia, recurrent painful episodes, strokes, nephropathy, retinopathy, avascular necrosis, priapism, and leg ulcers[5]. The foremost diagnostic modalities for SCD include a complete blood cell count, hemoglobin electrophoresis, and high-performance liquid chromatography (HPLC)[6]. Life expectancy is significantly diminished, with affected individuals often not surviving beyond an average age of 43 years[7]. In the United States, although a majority of children with SCD reach adulthood, their lifespan is typically reduced by approximately 20 years compared to the general population[5].

Current treatment options

Hydroxyurea

Hydroxyurea (HU) remains the foremost disease-modifying therapeutic option for SCD and has gained approval for administration in both pediatric and adult populations. The consistent demonstration of its clinical effectiveness and safety has led to its application even in very young children, aiming to mitigate acute and chronic complications[8–10]. While concerns persist regarding the potential long-term impacts of HU, particularly on fertility and reproduction, findings from a multicenter clinical trial evaluating fixed doses of HU in children aged 9–18 months revealed both safety and efficacy in reducing SCD-associated complications[9]. Consequently, HU is now recommended for all children with SCD aged 9 months and older, regardless of disease severity. Moreover, in older children, intensifying the dosage of HU is correlated with improvements in clinical and laboratory parameters compared to maintaining lower fixed doses[9,10]. Commonly reported adverse effects of HU include mild gastrointestinal discomfort, skin or nail darkening, and rarely, thinning of the hair[11].

Glutamine

Glutamine, an amino acid integral to nitrogen transportation and serving as a precursor for synthesizing vital compounds like glutathione, nicotinamide adenine dinucleotide, and arginine, is hypothesized to shield sickled red blood cells from oxidative injury. In 2017, the FDA endorsed the use of glutamine for individuals aged 5 years and older with SCD following findings from a randomized, placebo-controlled, multicenter, phase 3 trial. This trial revealed slight yet statistically significant decreases in acute sickle cell crises and related hospitalizations[12]. Glutamine is orally administered twice daily in powder form. Presently, information regarding the optimal dosage or specific laboratory monitoring protocols is lacking. Moreover, there is a need for enhanced clarity concerning the cost and availability of this treatment. Given the limited safety data and concerns regarding potential toxicity, particularly in patients with hepatic or renal impairment, cautious administration is recommended within this subgroup until more comprehensive safety data are available[13].

Emerging drug therapies

Ongoing studies are focusing on targeting diverse mechanisms involved in SCD. Crizanlizumab, a monoclonal antibody designed against P-selectin glycoprotein found on activated endothelial cells and platelets, aims to reduce the frequency of vaso-occlusive crises[14]. In January 2019, it received a breakthrough therapy designation for preventing vaso-occlusive crises in SCD patients. Subsequently, on 20 November 2019, the FDA approved crizanlizumab for individuals aged 16 and above with SCD[15]. Additionally, in January 2018, the FDA granted a breakthrough therapy designation to voxelotor, a hemoglobin S polymerization inhibitor, following preliminary clinical evidence indicating potential substantial improvement over existing therapies[16]. As a result, on 25 November 2019, voxelotor received accelerated approval for use in SCD patients aged 12 and older[15].

Transfusion therapy

The use of acute transfusion therapy in SCD is implicated in specific clinical circumstances. Prophylactic transfusions are recommended for surgeries that require general anesthesia, aiming to achieve a preoperative hemoglobin target of 10.0 g/dl in individuals with HbSS/Sb0[17]. Those with elevated baseline hemoglobin levels (HbSC/SB1) may necessitate exchange transfusions. Transfusion therapy proves beneficial in managing acute complications of SCD, such as stroke, acute chest syndrome, splenic sequestration, and other SCD-associated complications[17].

Hematopoietic stem cell transplantation

In 1984, the first recipient of hematopoietic stem cell transplant (HSCT) for SCD underwent the procedure for acute myeloid leukemia and experienced a cure for SCD as an unexpected outcome[18]. However, the variability in SCD presentations during childhood and the associated risks of transplantation have constrained the widespread adoption of HSCT. Recent reports on 1000 recipients of matched sibling donor (MSD)-HSCT revealed a 5-year overall survival (OS) rate of 92.9% and event-free survival (EFS) rate of 91.4%[19]. Although early post-HSCT mortality was relatively low in young children, it escalated with age, resulting in an EFS rate of 81% for recipients older than 16 years with MSD, and even lower rates after alternate donor transplants[19]. Some recipients experienced acute or chronic graft-versus-host disease (GVHD), potentially substituting one chronic condition for another. Unlike HSCTs performed for malignant conditions, GVHD does not serve any therapeutic purpose following HSCT for SCD. The delicate balance between benefits and risks underscores the challenging decisions that families and healthcare providers of SCD patients must confront, including the acceptance of elevated short-term risks, even with an ideal HLA-identical sibling donor, in pursuit of a potential cure[20].

Current treatment limitations and rationale for gene therapy

HU and glutamine stand as the sole FDA-approved medications for SCD treatment. However, these therapies do not entirely halt the progression of SCD into a chronic condition. Given the well-characterized monogenetic defect underlying SCD since its identification, SCD presents a promising candidate for gene-modifying or replacement therapies. Gene therapy emerges as an appealing avenue for achieving a cure, particularly considering that less than 20% of individuals with SCD possess a matched sibling donor for HSCT. Gene therapy approaches for SCD encompass replacing the defective beta-globin gene, enhancing HbF production through gamma-globin gene manipulation, or reactivating silenced gamma-globin genes[21–23]. To effectively cure SCD, gene transfer to the hematopoietic stem cell population must exhibit high efficiency and ensure sustained gene expression over the long term.

Casgevy: CRISPR/Cas9 breakthrough in SCD

The CRISPR/Cas9 system, an innovative and versatile genome editing tool, has emerged as a pivotal technology in the realm of genetic manipulation due to its efficacy and adaptability. The system consists of two essential components: the Cas9 protein, a programmable nuclease, and the single guide RNA (sgRNA), responsible for directing Cas9 to the targeted DNA site[24,25]. The orchestrated interplay between these components facilitates precise genome modifications. Upon introduction into cells, the CRISPR/Cas9 system induces double-strand breaks (DSBs) at the specified genomic location, subsequently activating DNA repair mechanisms. This process can lead to the generation of insertions or deletions (INDELs), resulting in the inactivation of a specific gene. Alternatively, homology-directed repair (HDR) may be employed, utilizing homologous DNA strands to mend the induced DNA breaks[24]. The simplicity of design, remarkable efficiency, and cost-effectiveness of this strategy have revolutionized genome editing techniques, opening avenues for its potential application in clinical settings. Casgevy stands as the first FDA-approved therapeutic application of CRISPR/Cas9, a revolutionary genome editing technology, designed for addressing SCD in patients aged 12 years and above, as well as in individuals experiencing recurrent vaso-occlusive crises.[26]. Through the administration of Casgevy, hematopoietic stem cells undergo precise modifications via the CRISPR/Cas9 methodology, enabling targeted alterations to specific DNA segments as shown in Figure.

In a clinical trial utilizing CRISPR-Cas9, researchers targeted the erythroid-specific enhancer region of the BCL11A gene in hematopoietic stem and progenitor cells (HSPCs). This targeted approach resulted in diminished BCL11A expression within erythroid cells, consequently resulting in an increased production of γ-globin[27]. The outcome of this genetic modification in long-term hematopoietic stem cells is a notable elevation in fetal hemoglobin levels, accompanied by a reduction in vaso-occlusive events, thereby obviating the need for transfusions[28]. HBF, crucial for efficient oxygen transport, plays a pivotal role in preventing sickling of red blood cells in patients afflicted with SCD.

Figure: Mechanism of action of CRISPR/Cas9 system (Created with Biorender.com).

Implications and benefits of Casgevy

Casgevy emerges as a groundbreaking intervention, representing the first gene therapy for SCD. Unlike conventional treatments, Casgevy holds the potential for a curative approach, promising recovery for a substantial number of patients[29]. A distinctive advantage of the therapy lies in its ability to prevent the necessity for recurrent blood transfusions and transplant procedures, thereby significantly enhancing the quality of life for individuals with SCD[30]. Furthermore, the risk of graft-versus-host disease is diminished, along with a decreased reliance on immunosuppressive medications, rendering Casgevy a safer alternative compared to conventional stem cell transplant methods[29,31]. In addition to its safety profile, the therapy demonstrates a potential reduction in vaso-occlusive events, a hallmark complication of SCD[28]. This multifaceted impact positions Casgevy as a transformative intervention, offering a secure and accessible alternative to the existing spectrum of treatments for SCD. In conclusion, while current FDA-approved treatments for SCD address specific aspects of the disease, they fall short of providing a comprehensive, stand-alone therapeutic solution. Casgevy, with its remarkable attributes of safety, curative potential, and impact on disease complications, emerges as a promising revolutionary treatment for SCD.

Ethical considerations and future prospects

The CRISPR technology presents significant potential for revolutionizing the field of medicine; however, its application introduces ethical quandaries that warrant careful consideration[32]. A central focus of ethical deliberations pertains to the manipulation of the human germline, as alterations made in this context would be heritable, contributing to the urgency of addressing associated ethical concerns[33]. While researchers and bioethicists collectively recognize the imperative for additional research to substantiate the safety and effectiveness of gene therapy, there exists a consensus that efforts to edit the human germline for reproductive purposes should be deferred[33]. The prospective benefits of Casgevy stimulate extensive discussions concerning societal equity and distributive justice, particularly in light of the substantial costs associated with its implementation[33].

Consequently, the establishment of comprehensive ethical and legal regulatory frameworks is deemed imperative to effectively address these societal concerns. Safety concerns about Casgevy predominantly revolve around potential mosaicism and off-target effects, necessitating an in-depth exploration of these issues[32]. A critical area requiring further investigation lies in ascertaining the therapy's long-term safety and efficacy, emphasizing the need for sustained research efforts[32]. Additionally, the exploration of combination therapies incorporating the CRISPR/Cas9 system is deemed crucial for identifying the most optimal treatment approach, particularly for conditions such as SCD[32]. However, it is imperative to acknowledge that managing ethical apprehensions associated with CRISPR intervention requires the formulation of future policies aimed at providing ethical guidance and ensuring responsible research and application of this groundbreaking technology. This underscores the necessity for ongoing interdisciplinary collaboration and ethical oversight to navigate the evolving landscape of CRISPR technology in medicine.

Conclusion

In essence, CRISPR/Cas9, exemplified by Casgevy, represents a pivotal advancement in SCD treatment. The findings from clinical trials, particularly targeting the erythroid-specific enhancer region of the BCL11A gene, have unveiled a promising future. The precise genetic modifications induced by Casgevy resulted in elevated HbF levels and a significant reduction in vaso-occlusive events. This revolutionary approach not only obviates the need for recurrent transfusions but promises a remarkable improvement in the quality of life for individuals grappling with the multifaceted challenges of SCD. However, as we celebrate this scientific triumph, ethical challenges are of paramount significance. The ability to edit the human germline demands careful ethical scrutiny and necessitates robust regulatory frameworks, requiring sustained interdisciplinary collaboration and ethical oversight. The journey from CRISPR's promise to its responsible application requires diligence, transparency, and a commitment to ensuring equitable access to this revolutionary technology. CRISPR/Cas9, with its safety, curative potential, and transformative impact, stands as a beacon of progress in medical science, signifying a paradigm shift in the management of SCD.

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Consent

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