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A REVIEW ON SICKLE CELL DISEASE: FROM CONVENTIONAL MANAGEMENT TO NOVEL THERAPHIES

Ms.Uma Dnyandev Kolhe[1], Mr. Arshad. A. Ansari[2], Dr. Sunil. S. Jaybhaye[3]

[1]*Student of Bachelor in Pharmacy, Dr Babasaheb Ambedkar Technological University, Raigad,lonere.*

[2]*Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Dr Babasaheb Ambedkar Technological University Raigad Lonere.*

[3]*Faculty of Pharmacy Department of Pharmaceutical Cology Dr. Babasaheb Ambedkar Technological University, Raigad Lonere.*

ABSTRACT

Millions of individuals worldwide suffer with sickle cell disease, a prevalent and sometimes fatal blood condition. Ischemia and inflammation, acute painful sickle cell crises, parenchymal damage, and persistent organ damage result from abnormal sickle-shaped red blood cells obstructing blood flow in small blood arteries. The polymerization of sickle hemoglobin (HbS), a sickling process that occurs inside these individuals' red blood cells (RBCs) during a deoxygenating state, is the primary physiological complication. The polymerization of mutant hemoglobin (HbS) within the RBC and membrane deformation under anoxic conditions are the causes of the RBC's transformation from spherical to sickle shape. The sickling process and mechanism are extremely intricate and multifaceted. Although stem cell transplantation may be a potentially curative therapy, gene therapy and gene editing are among the few treatments currently available, such as blood transfusions, certain medicines, and pharmaceuticals. Recent developments include better management, diagnostic tools, and systematic universal screening for stroke risk. Other options, such as traditional medicine in the form of medicinal herbs to manage the disease's symptoms, need to be looked into. The main efficient species for preventive treatment appear to include Cajanus cajan, Carica papaya, Piper guineense, aloe vera, allium sepa, Moringa oleifera, and Vinga unguiculata, all of which have anti-sickling qualities. Sickle cell disease (SCD) is a hereditary condition that affects worldwide health and has serious clinical implications. Survival has increased with traditional care techniques, but new treatments are changing the paradigm in favor of possible cures. This review reviews recent developments, such as gene editing and stem cell transplantation, summarizes well-established treatment modalities, and explores potential future approaches in SCD therapy .

KEYWORDS : *Anaemia- Sickle Cell, Sickle Cell Genetics, Complications, Screening Program, Recent Advance Treatment Methodology.*

INTRODUCTION

cell disorder, and sickling. A tetrameric protein is hemoglobin. Heme contains iron and porphyrin, and the quaternary protein structure (1, 2, and 1, 2) has heme + globin subunits. Eachheme group's ferrous ion atoms form a reversible bond with oxygen.[1] Erythropoiesis, leukopoiesis, and thrombopoiesis are all part of the haematopoiesis process, which produces erythrocytes, or red blood cells. Hb is expressed by red blood cells (RBCs) that are both mature (erythrocytes) and immature (reticulocytes). Different types of Hb are typically expressed at different periods of life: HbA for adults and HbF for embryos and fetuses. The sickle hemoglobin is caused by a single nucleotide mutation in HBB, which is known as the HbS allele (mutant hemoglobin component). The sickled shape of the erythrocytes is caused by Hb tetramers with two mutant HbS polymers. Vaso-occlusive events may result from sickle erythrocytes. [3] Saudi Arabia, Yemen, India, Pakistan, Bangladesh, China, the United States, Europe, and Sub-Saharan Africa are among the African nations where SCA is most prevalent worldwide. [4.5]

In the steady state, the majority of children with sickle cell anemia maintain a hemoglobin concentration of 7 to 8.5 g/dl.

The WHO estimates that 4.5% of people worldwide have sickle cell genes. The mortality rate for infants with sickle cell disease (SCD) is 1% in the United States, but it can reach 90% in places with few medical facilities and 50% in places with better health infrastructures. The RFLP (Restriction Fragment Length Polymorphism) evaluated five SCD haplotypes, named according to where they originated. The HbF levels can be linked to the following haplotypes: Senegal & Arab-Indian, Benin/Bontu, compared to CAR (Central Africa Republic), and Cameroon. The dispersion of erythrocytes can affected HbF level.Due to geographic spread, societal barriers, healthcare facilities, a huge population, an increasing birth rate, and consanguineous marriage, sickle cell disease causes a high prevalence of morbidity and mortality in India. It puts the indigenous populations in jeopardy. is derived from the Latin word "tribus," which means "a group of persons forming a community and claiming descent {ADIVASI, VANYAJATI, VANVASI, PAHARI, ADIMJATI aur ANUSUCHIT ANJATI.}from a common ancestor." According to the constitution, the tribes are referred to as. Recent migration trends are linked to SCD in non-malarial areas. bSS [homozygous state] Although the precise process is uncertain, a number of investigations have shown that the ringparasitized red

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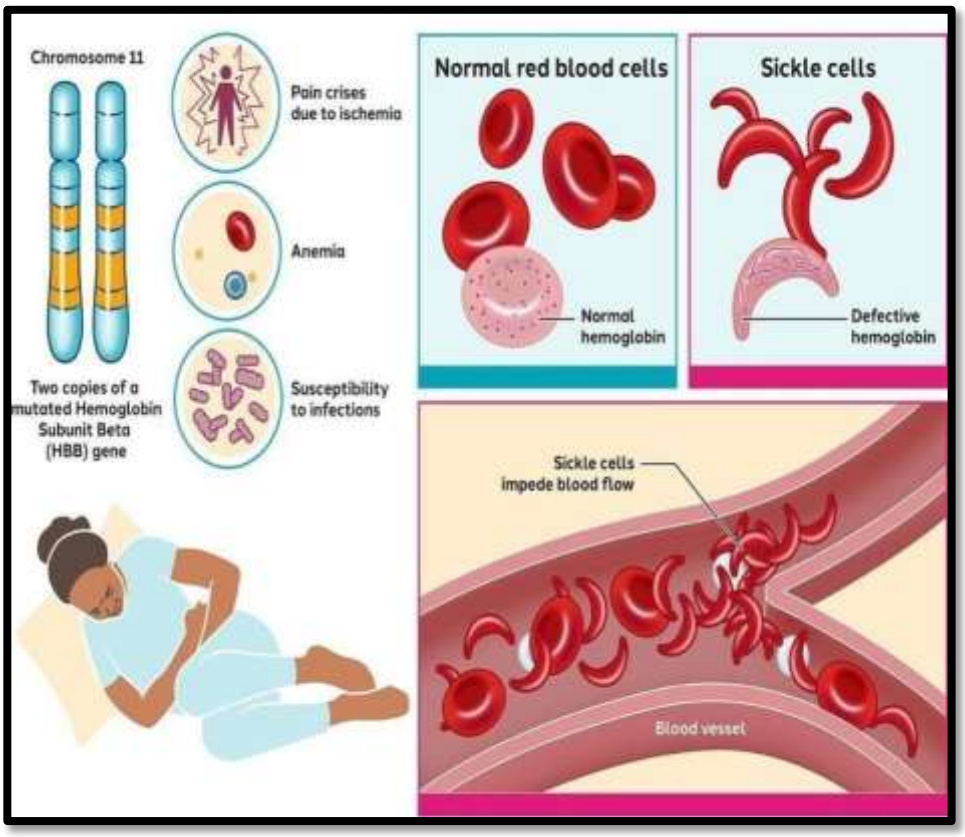
blood cells in sickle cell trait patients.

Anatomy

Sickle cell anemia is a hereditary hemoglobin disorder characterized by the presence of abnormal sickle-shaped red blood cells (RBCs) due to a structural defect in the hemoglobin molecule (HbS).

2. Anatomical Basis



STRUCTURE OF SICKLE CELL ANEMIA

Cellular Anatomy

Normal RBCs are biconcave discs, flexible, and about 7–8 µm in diameter.

- In sickl cell anemia, RBCs contain Hemoglobin S (HbS) instead of normal Hemoglobin(HbA).
- Under low oxygen tension, HbS polymerizes, causing RBCs to become elongated, crescent (sickle)-shaped, and rigid.
- These altered cells lose flexibility, leading to vascular blockage and tissue ischemia.

Blood And Vascular System Anatomy

- Microcirculation: Sickled RBCs obstruct small capillaries and venules, leading to local tissue infarction.
- Blood viscosity increases due to abnormal RBC shape and decreased deformability.
- Endothelial injury occurs in small vessels because of repeated mechanical trauma by rigid sickled cells.

Orgon anotomy change Organ Anatomical Changes Spleen
Initially enlarged due to congestion (splenomegaly); later shrinks and becomes fibrotic — autosplenectomy.
Hyperplasia of erythroid precursors due to increased RBC destruction — causes expansion of marrow cavities and "crew-cut" appearance of skull bones on X-ray. Liver
Congestion and hemosiderosis due to hemolysis; may show hepatomegaly. Kidney Heart Cardiac enlargement from chronic anemia (compensatory).

Bones and Joints
Infarctions lead to pain and deformities; avascular necrosis (especially femoral head).

Microscopic Anatomy

- Peripheral Blood Smear:
- Sickle-shaped erythrocytes
- Target cells
- Howell–Jolly bodies (due to splenic dysfunction)
- Spleen Histology: Fibrosis, atrophy, hemosideric deposition, loss of splenic architecture.
- Bone Marrow: Hypercellular with erythroid hyperplasia.

Summery

The anatomical hallmark of sickle cell anemia is the distortion of RBC morphology into a sickle or crescent shape, leading to widespread vascular obstruction, organ ischemia, and tissue damage throughout the body — particularly in the spleen, bone marrow, and vasculator.

Pathophysiology

Content And Pathophysiology

Sickle cell disease, a collection of hereditary hemoglobin disorders (primarily due to the Hb S mutation in the β-globin

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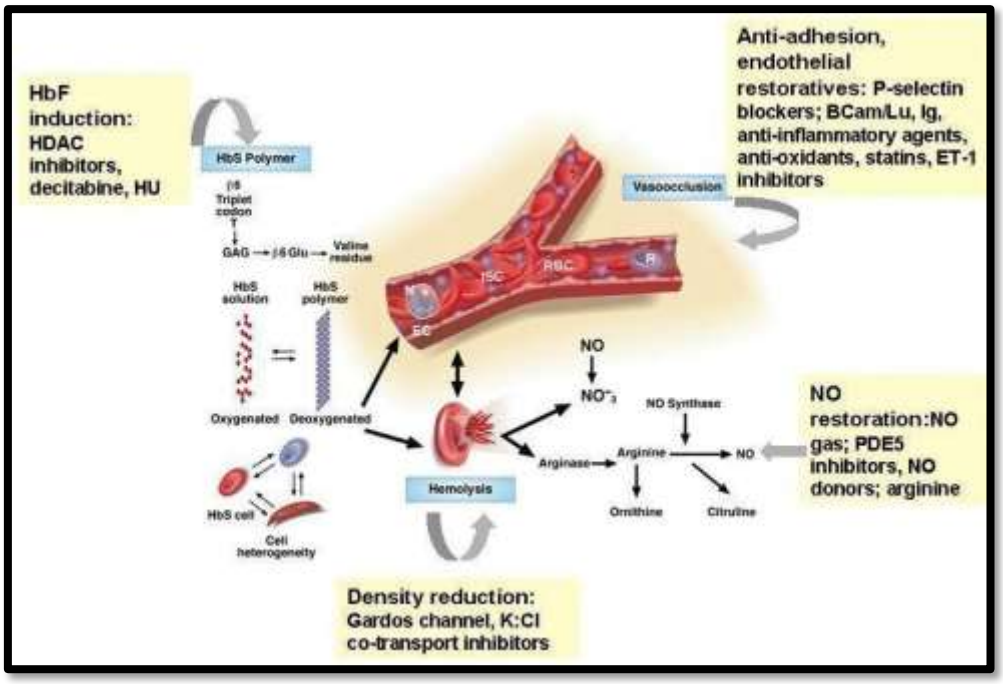
gene), leads to red-cell sickling, hemolysis, vaso-occlusion, organ damage, abnormal deoxygenated hemoglobin polymerization, and reduced lifespan. The alteration in the β-globin gene (HBB) results in a glutamic acid → valine exchange in the β chain; at low oxygen levels, HbS forms polymers. alters RBC shape, heightens rigidity, and reduces RBC lifespan. Sickled cells increase adhesion to endothelial cells, elevate oxidative stress, raise inflammation, and result in vasoocclusive crises (pain episodes), acute chest syndrome, stroke, and chronic organ damage. The global impact of the illness is considerable — highest rates are found in regions that traditionally have endemic malaria (sub-Saharan Africa, the Middle East, areas of India, and South Asia). The global disease burden is significant — the highest prevalence occurs in regions historically affected by malaria (sub-Saharan Africa, the Middle East, and certain areas of India and South Asia). For instance, the WHO approximates that around 7.74 million individuals are living with SCD. Due to the multi-factorial nature of the pathophysiology (hemolysis → anemia + vaso-occlusion + endothelial activation + oxidative stress + inflammation + organ damage), it provides several targets for intervention.



Structure Of Pathophysiology Disease (Figure)

Traditional / Recognized Management

These are the presently recognized, commonly employed treatment and supportive care methods for SCD. A. Preventive and supportive care includes newborn screening when accessible, and penicillin prophylaxis (particularly in children) to lower the risk of invasive pneumococcal disease. Immunizations (e.g., pneumococcal, Haemophilus influenzae, meningococcal) administered due to the risk of functional asplenia. Supplementation of folic acid (resulting from heightened RBC turnover). For instance, Indian national guidelines highlight the importance of folic acid (5 mg daily for those over one year of age) in SCD. Drinking plenty of water, following conventional procedures for managing discomfort, and keeping an eye out for any consequences (such as screening youngsters for stroke or Transfusion therapy: continuous transfusion in certain situations (e.g., primary or secondary stroke prevention) and episodic for acute consequences (stroke, acute chest syndrome). When repeated transfusions result in iron excess, iron chelation occurs. Maintaining a healthy lifestyle includes avoiding excessive temperatures and dehydration, controlling infections, and managing acute situations quickly.

2. Specification And Modern Therapy

The primary disease-modifying medication has been hydroxyurea, commonly known as hydroxycarbamide. It has been demonstrated to lessen pain episodes, acute chest syndrome, and the need for transfusions. It also raises fetal hemoglobin (HbF) levels, decreases white cell and reticulocyte counts, and lessens sickling. Hydroxyurea dosage and monitoring recommendations for sickle cell disease (SCD) have recently been produced by guidelines like For certain patients, transplantation (haematopoietic stem cell transplantation, HSCT) from matched donors is a curative possibility (lower age, less organ problems, donor availability).

Appropriate transplant indications are outlined in the earlier guidelines (such as the National Heart, Lung, and Blood Institute's 2014 panel).

3. Acute Circes Management

Vaso-occlusive pain crisis: treat precipitating conditions (infection, dehydration), administer analgesia (typically opioids), water, and oxygen if necessary. Oxygen, antibiotics, transfusions, and occasionally exchange transfusions are used for acute chest. Syndrome Stroke: both acute treatment and long-term therapy to avoid recurrence. Organ-specific: screening for pulmonary hypertension, kidney monitoring, etc. Indian operating guidelines state that "the goal is patient- centric focusing on life-course approach once the individual is confirmed positive." prevent and lessen the occurrence of

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problems and catastrophes. handle problems and crises in a timely and efficient manner.
Worldwide, for instance, preventive and monitoring measures are covered in WHO guidelines for SCD in pregnancy.

4. Novel And Emerging Therapy
Novel therapies with various mechanisms of action, such as targeting Hb S polymerization, increasing HbF, reducing adhesion/vaso-occlusion, gene therapy/editing, modulating oxidative stress/inflammation, etc., are being developed because conventional therapy still leaves many patients with significant morbidity and shorter life expectancy. While some have received regulatory approval in specific regions, many are still undergoing clinical studies.

5. New And Development Treatment
Novel therapies with various mechanisms of action, such as targeting Hb S polymerization, increasing HbF, reducing adhesion/vaso-occlusion, gene therapy/editing, modulating oxidative stress/inflammation, etc., are being developed because conventional therapy still leaves many patients with significant morbidity and shorter life expectancy. While some have received regulatory approval in specific regions, many are still undergoing clinical studies One such licensed treatment (in some areas) that binds to hemoglobin and changes its affinity to lessen sickling is voxelotor, a HbS polymerization inhibitor. It is covered in reviews of novel and up treatment.

Curative – Gene Therapy & Transplantation
Hematopoietic stem cell transplant (HSCT) remains the only widely established curative therapy, though constrained by donor availability, risk of graft-versus-host disease (GVHD), etc. The field is evolving with less-intensive conditioning, haplo-donor transplants, etc.

Gene Editing/Therapy represents a thrilling new frontier:
A clinical trial ("RUBY Trial") using CAR or CRISPR-based editing (e.g., EDIT-301 editing patients' own stem cells) has shown initial results: in the first four patients, normal haemoglobin levels, no sickle-cell pain ises for months, and no severe adverse effects reported.

Also, a genome-wide association study identified new genetic targets (e.g., the FLT1 gene) that regulate fetal haemoglobin levels and may broaden the possibilities of gene-editing therapy in the future.

Feature Direction and Challenges
Many future therapies are still early phase, and major challenges exist: cost, infrastructure, accessibility (especially in low- and middle-income countries where most SCD burden is). The review by Kuriri (2023) "Hope on the Horizon: New and Future Therapies for Sickle Cell Disease" provides an overview of many of these future paths (HbF induction, HbS polymerisation inhibitors, cell therapies) and emphasizes the unmet needs. Also the 2024 Cells review emphasises categorising therapies by their targets: curative, HbS polymerisation, downstream effectors.

Transitioning from Traditional to Innovative: connecting the divide
Putting it all together, we can map the shift from conventional management toward novel therapies, identify unmet needs, and discuss implications. A single nucleotide of the HbB allele is replaced with the HbS allele at the beta-position of the globin molecule GAG-GTG (glutamic acid to valine) in sickle cell anemia, a hereditary disease. SCD affects several nations, including those in Africa, Saudi Arabia, Yemen, India, Pakistan, Bangladesh, China, the United States, Europe, and more. SCD cases are seen in several Indian states and castes, primarily in Odisha, Maharashtra, MP, CG, Bihar, Assam, and Gujarat. In Chicago, the first SCD case was discovered between 1904 and 1906. The sickle shaped RBCs are loss their elasticity and rigidity, hence they cannot flow easily in blood vessels and then causes vasoocculusion pressure, joint pain, stroke, chest pain, and other sign and symptoms like Fatigue, Shortness of breath.

Why Conventional Therapy Foll Short
Even with hydroxyurea and optimized supportive care, many patients continue to have frequent pain crises, organ damage, and reduced life expectancy (often mid-40s in many settings).

Access issues: In many low-income settings, newborn screening, penicillin prophylaxis, transfusion services, iron chelation, and hydroxyurea are not uniformly available. Curative options (HSCT) are limited by donor availability, risk/benefit concerns, and cost. Therefore, there is a substantial unmet need for therapies that are more effective, less burdensome (e.g., oral, once-in-lifetime), and accessible.

How new treatments target particular pathophysiologic targets
Voxelotor and other HbS polymerization inhibitors specifically target the sickling root mechanism.
The protective effect of HbF (fetal hemoglobin) against sickling is addressed by HbF-induction therapy (hydroxyurea is one; new ones aim for more HbF, better safety/efficacy). Treatments that alter adhesion, inflammation, and oxidative damage are intended to lessen organ damage and vaso-occlusion downstream of the sickling. The goal of gene therapy/editing and HSCT is to either cure or almost cure the underlying ailment by replacing or correcting the faulty β- globin gene (or increasing HbF expression). For instance, by increasing targetability, genome wide association (FLT1) genetic targets maymake gene treatments accessible to more individualsThe outcome is a gradual transition from"manage complications + supportive care".

Risk Factors
- Sickle cell anemia Sickle cell anemia is an inherited genetic disorder caused by mutations in the hemoglobin subunit beta gene that encodes the beta globin chain of hemoglobin. The main risk factor for developing sickle cell anemia is genetic inheritance though environmental and clinical factors can exacerbate the disease.

Intestinal Disorder
Having an intestinal disorders that affects the absorption of nutrients in small intestine such as crohn disease and celiac

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disease surgical removal the part of small intestine where nutrients are absorbed can lead to nutrient deficiencies and Anemia.

Family History

A family history of sickle cell disease or carriers of sickle cell trait increases the likelihood of inheriting the disease genetic counseling is advised for family with a history of Sickle cell disease to understand the inheritance patterns are risk for offspring.

Environmental and Clinical Factors

Low oxygen condition or high altitudes can exacerbates the sickling of red blood cells and trigger vasooclusive crises.Infection sickle cell are increased risk of infection particularly from streptococcus pneumoniae,Haemophilus influenzae and neisseria meningitis due to increase the risk of severe infection.Dehydration and extreme physical stress can also trigger sickling and exacerbate symptoms leading to episode of pain or other complications.

Conventional and Hydroxyurea Method

Hydroxyurea

continues to be the fundamental treatment for SCD, promoting fetal hemoglobin production and decreasing the occurrence of painful crises. Prolonged use has indicated a lower risk of stroke and enhanced survival, although worries regarding myelosuppression remain.[14]

Blood Donation

Consistent blood transfusions avert stroke and address acute anemia. Risks encompass iron excess and alloimmunization, addressed through chelation therapy and meticulous matching.[15]

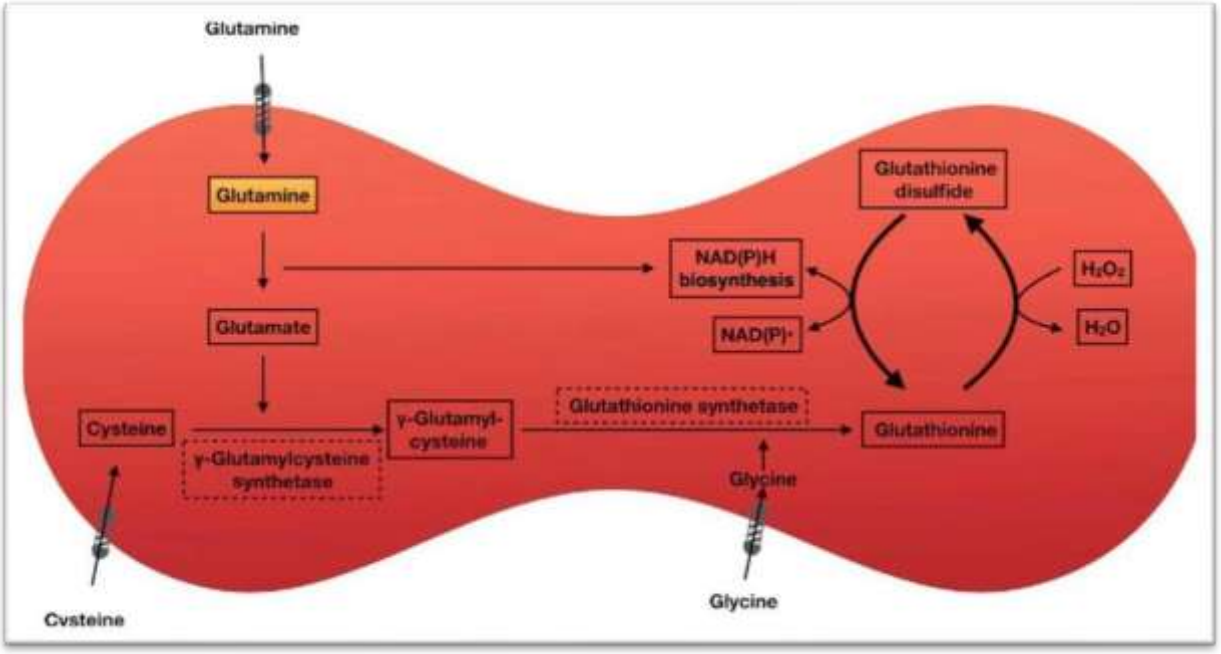
Pain Relief and Supportive System

Multimodal pain management—incorporating NSAIDs, opioids, and non-drug approaches— continues to be crucial. Immunizations, disease prevention, and regular health care improve life quality. [15]

Advancements of Treatments

New Anti sickling Compounds

The polymerization of hemoglobin S is the initial stage in the sequential pathophysiology of SCD. Agents inhibit the polymerization of Hemoglobin S. that stimulate HbF (e.g., hydroxyurea [mentioned decitabine, pomalidomide, panobinostat, INCB059872, and sodium butyrate were mentioned, dissua polymerization by inhibiting dehydration (senicapoc and magnesium), postpone the formation of deoxyhemoglobin S by altering the oxyhemoglobin dissociation curve shifts to the left (increasing Hb's affinity for oxygen, e.g., Aes103 and GBT440), provide carbon monoxide to the RBC (pegylated



Mechanism Of Action

carboxyhemoglobin),61 and prevent sickling through an unidentified mechanism (SCD-101 and Nicosan). SCD-101, an innovativebotanical medication with an unclear mechanism exhibits a dose-dependent effect against sickling. It seems that your input got cut off. Please provide the complete text you'd like me to paraphrase. phase 1b dose-increasing trial involving individuals with SCA, SCD-101 was well tolerated and reduced . persistent discomfort and exhaustion.62 Section B of thisstage1b clinical trial is a randomized, double- blind study, placebo-controlled crossover trial of SCD-101 in individuals with SCA and is presently enrolling (NCT02380079). An additional antisickling agent Nicosan operates through a mechanism of action that is not fully understood. (or Niprisan) is a botanical extract demonstrated to lower suffering episodes in Nigerian patients.There are no research on Niprisan is being conducted in the United States. Clinical trials examining the use of the previously mentioned agents are recruiting participants.[18]

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Long Time transfusion - Therapy
treatment with RBC transfusion serves as an alternative to hydroxyurea. Compelling evidence supports long-term RBC transfusions for children with HbSS and abnormal TCD to avert strokes. The multicenter Stroke Prevention Trials in Sickle Cell Anemia (STOI and II) indicated that extended transfusion therapy in children with abnormal TCD diminished stroke risk, and this beneficial effect ceased.

when transfusions were discontinued. The Stroke With Transfusions Changing to Hydroxyurea (TWITCH) trial demonstrated that switching from ongoing transfusion therapy to hydroxyurea at the highest tolerated dose in children with abnormal TCD but without severe vasculopathy was not less effective. than continuous transfusions and could serve as an alternative for primary prevention of cerebrovascular disease. Chronic transfusion therapy is carried out as straightforward transfusions or partial or full exchange transfusions (erythrocytapheresis). Long-term transfusion therapy carries risks such.as transfusional iron overload (lesser with exchange transfusions), which builds up over time and can be life-threatening, alloimmunization, and the potential for transmission of transfusion- related infections. Delayed hemolytic transfusion reactions due to alloimmunization complicate 4% to 11% of transfusions for SCD.[19] **Gene Therapy is Considered:** the "Holy"Grail" of SCD therapy and has persisted as pursued as a final solution. In 2017, Ribeil et al93 documented a 13-year-old male who Gene therapy has cured HbSS disease. This exciting occasion signified the initial instance an antisickling β-globin variant (βA-T87Q) possessed has been effectively implanted in a human recipient. Recent advancements in technology, such as in situ gene alteration (e.g., through CRISPR/ Cas9) is generating possibilities for genetic manipulation (gene insertion, deletion, or modification) by removing the HbS mutation or boosting HbF synthesis by silencing a inhibitor of HbF synthesis (e.g., BCL11A).94,95 Following the promotion of mouse research on gene therapy,96,97 two clinical trials examining gene therapy employing a lentiviral vector in adults with homozygous or serious variant SCD is ongoing method (NCT02247843, NCT02186418).

Additional research is required to validate this treatment's sturdiness and security. A myeloablative conditioning protocol succeeded by the administration of manipulated self- derived stem cells is beneath inquiry.[16][20]

Hydroxycarbamide
Hydroxyurea was the initial drug approved by the US Food and Drug Administration (FDA) authorized medication for the management of homozygous SCD and is the sole therapy that alters the progression of the disease and is backed by strong proof in kids and adults. Hydroxyurea acts as a ribonucleoside diphosphate reductase. inhibitor initially employed as a cytoreductive treatment for myeloproliferative disorders. Hydroxyurea boosts the production of fetal Hb (HbF; a2g2) and reduces the polymerization of intracellular HbS, an impact that is maintained with extended use but is reversible upon stopping the medication. The finding that hydroxyurea boosts HbF levels resulted in preliminary testing of the medication in individuals with HbSS.

Additional cellular advantages from hydroxyurea for individuals with homozygous SCD involves a reduction in leukocytes, platelets, and counts of reticulocytes and alterations in the expression of cellular, inflammatory, and adhesion molecules which diminish abnormal cellular adhesion and inflammation. Research in both adults and children backing the application of hydroxyurea in homozygous sickle cell disease resulted in the FDA approving hydroxyurea for adults almost two decades prior and for kids.[21]

Novel Therapy: (Innovative Treatment) Traditional Gene treatment
L-glutamine and voxelotor (an inhibitor of HbS polymerization) have broadened treatment choices, with data indicating enhanced anemia and fewer crises. Pyridoxamine along with additional anti-inflammatory compounds is currently undergoing clinical development.

Novel Pharmaceutical Compound
L-glutamine and voxelotor (an inhibitor of HbS polymerization) have broadened treatment choices, with data indicating enhanced anemia and fewer crises. Pyridoxamine along with additional anti-inflammatory compounds is currently undergoing clinical development.[17]

Conversation
Comparative analyses emphasize hydroxyurea's significance in standard treatment, yet gene therapy and stem cell transplantation may transform therapeutic approaches for suitably chosen patient. Despite the presence of cost, safety, and implementation challenges, new agents are broadening disease-modifying advantages to additional populations.

DISCUSSION

Comparative studies highlight hydroxyurea's role in standard care, but gene therapy and stem cell transplantation could redefine treatment paradigms for appropriately selected patients[8][6][7]. While cost, safety, and implementation barriers exist, novel agents are extending disease-modifying benefits a more populations anemia a genetic disorder and characterized by the mutation on the sequence of haemoglobin chainat beta-position of globin molecule GAG-GTG (glutamic acid to valine), single nucleotide of HbB is substituted with HbS allele. Many countries are affected with SCD such as African countries, Saudi Arabia, Yemen,

India, Pakistan, Bangladesh, china, US, Europe etc. In India many states and several casts affected with SCD cases mostly in Odisha, Maharashtra, MP, CG, Bihar, Assam, Gujarat. The first case of SCD is found in Chicago at 1904-1906. The sickle shaped RBCs are loss their elasticity and rigidity, hence they cannot flow easily in bloodvessels and then causes vasoocculusion pressure, joint pain, stroke, chest pain, and other sign and symptoms like Fatigue, Shortness of breath, Dizziness, Headache, Coldness in the hands and feet, Pale skin, sometimes it may leads to organ damage. To avoid this complications many preventive therapies are available like gene.

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Current Advancement Therapy

(1) Modifying the Patient's Genotype

Modifying the patient's genotype via hemopoietic stem cell transplantation (HSCT) was first reported to be performed over 30 years ago in an 8-year-old child who had SCD (HbSS) with frequent VOCs; she subsequently developed acute myeloid leukemia. The patient received HSCT for the acute myeloid leukemia from an HLA-matched sister who was a carrier for HbS (HbAS). She was cured of her leukemia and at the same time, her sickle cell complications also resolved (Johnson et al., 1984; Johnson, 1985). Until then, HSCT had not been considered as a therapeutic option for SCD. This successful HSCT demonstrated.

CONCLUSION

Disease-modifying treatments for SCD comprise hydroxyurea, which is now FDA approved for both adults and children with homozygous SCD, as well as longterm blood transfusions. Almost 20 years after hydroxyurea received approval, Lglutamine gained FDA approval despite limited peer-reviewed evidence and numerous unresolved questions regarding its application and tolerability. Gene therapy for anti-sickling is a fascinating and hopeful research field but has not yet been proven safe or effective. Allogeneic HSCT remains the sole curative option and has recently demonstrated potential in older adults as well. Prompt referral for assessment for HSCT is highly recommended for patients experiencing symptomatic SCD. A need exists for therapies that modify diseases in SCD, along with significant recent scientific discoveries, has prompted the creation and evaluation of new agents currently undergoing preclinical and clinical trials. In the upcoming decades, these innovative strategies, when refined, could significantly enhance the prospects for individuals with SCD, their families, and their healthcare

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