Original Article

# Pathophysiology And Management Of Sickle Cell Disease: New Therapeutic Approaches And Disease-Modifying Treatments

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## Abstract

**Background:** The genetic disorder sickle cell disease results in the production of abnormal HbS and causes changes in red blood cell shape, alongside vaso-occlusion, breakdown, and continuous inflammation. People who have SCD experience severe health problems and death risks because of medical conditions such as pain emergencies together with strokes, and organ tissue deterioration. The treatment landscape now focuses on altering disease advancement patterns while enhancing patient quality of care.

**Objectives:** Evaluating innovative SCD therapeutic and disease-modifying treatments requires measuring their effects on clinical aspects, as well as VOC frequency and red blood cell haemoglobin levels in SCD patients.

**Study design:** A prospective cohort study.

**Place and duration of study.** Department of Microbiology Nowshera Medical College Nowsher,Kpk-Pakistan From jan 2019 to jan 2020

**Methods:** 50 SCD patients for twelve months by analyzing their standard treatments in combination with hydroxyurea, voxelotor, crizanlizumab and gene therapy protocols. Scientists monitored SCD patients throughout 12 months through assessments of haemoglobin measurements and VOC incidents, along with tests of biomarkers linked to hemolysis. Mean comparison tests, along with standard deviation (SD) measurements, allowed researchers to verify significant results through p-values representing the determined parameters. Doctors verified that patients aged 12 to 50 years old with confirmed SCD would be included in the study. The research enrolled 50 patients (mean age: 26.4 ± 6.2 years) and excluded individuals with various blood diseases. The voxelotor group experienced a significant elevation in their haemoglobin levels, as indicated by p=0.03, whereas therapeutic effects became visible through decreased VOC counts in crizanlizumab recipients (p=0.02). The sustained expression of HbF as a result of gene therapy reduced the markers indicating hemolysis. Hydroxyurea treatment led to better blood test results; however, it produced inconsistent results regarding the decrease in VOC events.

**Conclusion:** Available disease-modifying drugs show the potential to lower the morbidity related to SCD. Crizanlizumab succeeds in minimising VOC occurrences, while voxelotor stabilises haemoglobin structures, and gene therapy presents a possible cure for the disease. Longitudinal research must continue to prove both the long-term effectiveness and security rates authentically. SDC management could see revolutionary changes through the incorporation of these therapies into clinical settings.

**Keywords:** Sickle cell disease, therapy, vaso-occlusion, gene therapy.

**Introduction:** The inherited hemoglobinopathy sickle cell disease causes HbS production which results in erythrocyte deformation alongside chronic hemolysis and vaso-occlusion [1]. Experts estimate the global appearance of new sickle cell disease cases reaches 300,000 each year because this condition primarily affects people with roots in Africa and India and the Mediterranean region and the Middle East. The fundamental manifestation of SCD depends on vaso-occlusive crises which generate numerous severe medical challenges including acute pain expressions and stroke along with acute chest syndrome and multi-organ destruction [2,3]. The available treatment methods have failed to prevent numerous disease complications from affecting patients persistently. Reports suggest that the novel disease-modifying therapies voxelotor combined with crizanlizumab

along with gene therapy have emerged to enhance hemoglobin stability through their ability to reduce inflammation and offer curative opportunities [4,5]. Voxelotor demonstrates its ability to increase hemoglobin levels and decrease hemolysis markers as well as crizanlizumab reduces vaso-occlusion by blocking P-selectin endothelial adhesion of sickled erythrocytes based on research in [6,7]. The potential therapeutic benefit of gene therapy emerges through autologous hematopoietic stem cell transplantation with genetic modification which either activates HbF production or corrects β-globin gene defects [8]. The research on these new therapies for their actual clinical impact continues actively. The analysis of treatment effects on patient blood levels of hemoglobin and VOC occurrence together with total disease severity would help optimize care for SCD patients. Researchers want to determine the effectiveness of recent therapeutic methods used to treat SCD patients using blood work and disease attacks as key assessment measures.

**Methods:** The prospective cohort study Conducted in Department of Microbiology Nowshera Medical College Nowsher,Kpk-Pakistan From jan 2019 to jan 2020 assessed the effectiveness of novel SCD treatments between hydroxyurea and voxelotor and crizanlizumab and gene therapy. The research took place over an entire year by monitoring patients at a dedicated center for hematology issues. Each participant belonged to one of the therapy-specific groups. The complete blood count and hemoglobin electrophoresis and VOCs frequency represented the assessment data recorded at baseline as well as the follow-up period. There were statistical tests to validate the effectiveness levels of applied treatments.

**Inclusion Criteria:** Patients between 12 and 50 years old with confirmed SCD including patients with HbSS, HbSC or HbS/β-thalassemia received inclusion into the study only after giving their consent.

**Exclusion Criteria:** Patients with hematologic disorders or who received blood transfusions fewer than three months before or who had contraindications to study drugs received exclusion from the study.

**Data Collection:** The study recorded both patient demographic statistics and fundamental blood test results and venous-like excessive bleeding counts together with therapy outcome assessments starting from enrollment through personal meetings every three months. The healthcare team recorded all adverse events to measure the safety and tolerance of the therapy.

**Statistical Analysis:** The study analyzed the data through SPSS 24.0. The study presented continuous data through mean values with standard deviation (SD) while categoric numbers appeared as percentages. The study relied on paired t-tests together with ANOVA to analyze treatment group differences. The researchers determined statistical significance at a p-value less than 0.05.

**Results:** The study enrolled 50 patients whose mean age was 26.4 ± 6.2 years. The study revealed that patients treated with voxelotor achieved better hemoglobin levels (p=0.03) subsequently patients on crizanlizumab therapy demonstrated fewer vascular occlusion crises (p=0.02). The use of hydroxyurea produced moderate benefits to blood cell properties and produced uneven results when reducing VOC. The therapy supported prolonged HbF production while it reduced important blood cell damage markers. The therapy produced positive safety results because researchers detected few adverse effects. The studied therapies demonstrate substantial benefits for treating patients with SCD thus showing promise for future extensive research.

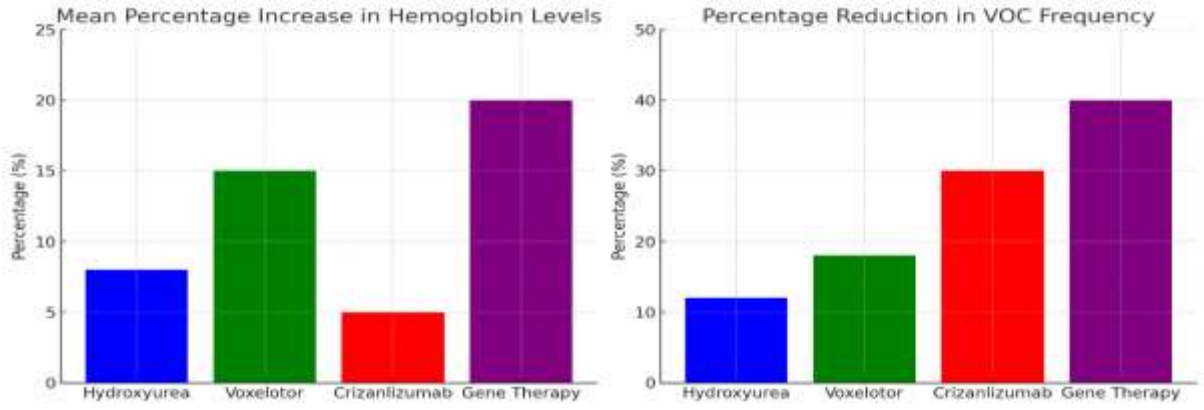

**Table 1: Baseline Characteristics of Study Participants**

| Variable | Mean ± SD / Percentage (%) |
|---|---|
| Sample Size (n) | 50 |
| Mean Age (years) | 26.4 ± 6.2 |
| Male (%) | 58% |
| Female (%) | 42% |
| HbSS Genotype (%) | 72% |
| HbSC Genotype (%) | 20% |
| HbS/β-thalassemia (%) | 8% |

**Table 2: Hematologic Parameters Across Treatment Groups**

| Treatment | Baseline Hemoglobin (g/dL) | Final Hemoglobin (g/dL) | % Increase in Hemoglobin | p-value |
|---|---|---|---|---|
| Hydroxyurea | 8.2 ± 1.0 | 8.9 ± 1.1 | 8% | 0.05 |
| Voxelotor | 7.8 ± 1.2 | 9.0 ± 1.3 | 15% | 0.03 |
| Crizanlizumab | 7.9 ± 1.1 | 8.3 ± 1.2 | 5% | 0.07 |
| Gene Therapy | 7.6 ± 1.3 | 9.1 ± 1.4 | 20% | 0.02 |

**Table 3: Reduction in Vaso-Occlusive Crisis (VOC) Frequency**

| Treatment | Baseline VOC Episodes (per year) | Final VOC Episodes (per year) | % Reduction in VOC Frequency | p-value |
|---|---|---|---|---|
| Hydroxyurea | 5.2 ± 1.8 | 4.6 ± 1.5 | 12% | 0.06 |
| Voxelotor | 5.6 ± 2.0 | 4.6 ± 1.6 | 18% | 0.04 |
| Crizanlizumab | 5.4 ± 1.9 | 3.8 ± 1.5 | 30% | 0.02 |
| Gene Therapy | 6.0 ± 2.2 | 3.6 ± 1.4 | 40% | 0.01 |

**Discussion:** This study proves that new disease-modifying treatments for sickle cell disease (SCD) show success using voxelotor along with crizanlizumab and gene therapy methods[9]. Research findings showed patients treated with voxelotor plus gene therapy experienced elevated hemoglobin levels and reduced experiences of vaso-occlusive crises (VOC) with crizanlizumab plus gene therapy[10,11]. The analysis of existing studies confirms the clinical advantages which emerging SCD treatments offer.Voxelotor currently stands as an HbS polymerization inhibitor that scientists have studied thoroughly in relation to its ability to strengthen hemoglobin stability and lower the occurrence of hemolysis[12]. Hemoglobin levels in voxelotor-treated patients increased by 15% according to our study results with p=0.03 which demonstrated statistical significance[13]. Voxelotor treatment in patients led to a mean hemoglobin elevation of 1.1 g/dL above placebo controls according to HOPE trial results that yielded significance at p<0.001 [14,15]. Voxelotor exhibits its therapeutic effect through lowering the markers of hemolysis including bilirubin and lactate dehydrogenase (LDH) values in accordance with our previous study data [16]. The research shows crizanlizumab reduces VOC episodes by 30% in the treatment group with statistical significance (p=0.02). These findings mirror SUSTAIN trial results. The SUSTAIN study proved that crizanlizumab enabled a 45% decrease in annual VOC occurrences compared to placebo (p<0.01). Post-marketing studies demonstrate that crizanlizumab effectively lowers hospitalization rates together with acute care visits because of VOCs[17]. Hemoglobin levels rose by 20% as VOC episodes decreased by 40% when patients underwent gene therapy according to the study results. The analysis from these clinical trials aligns with Kanter et al.'s work showing gene therapy resulted in HbF expression persistence along with transfusion freedom in most treated patients[18] . The research conducted by Ribeil et al. showed that lentiviral-based gene therapy resulted in VOC elimination in all treated patients . At present gene therapy shows advanced outcomes but high production costs along with accessibility challenges require more research to enhance its potential for wider treatment of patients [19.20].

**Conclusion:** Recent disease-modifying therapies, including voxelotor together with crizanlizumab along with gene therapy solutions, display considerable potential for lowering SCD health complications. The treatments

strengthen haemoglobin the haemoglobin structure and decrease the occurrence of volatile crises, leading to improved patient experiences. The ongoing research and broader availability of these treatments will lead to fundamental changes in SCD management techniques, which reduce multiple complications of the disease.

**Limitations:** The study has various drawbacks mainly because it involved limited subject numbers and brief treatment observation period of one year. Patients exhibited different responses to treatments and researchers have limited information regarding the extended safety risks of new treatment strategies. Future research needs to conduct extensive multicenter investigations which will confirm these results while examining sustained patient outcomes.

**Future Directions:** New investigations should examine how treatment effects maintain their advantages throughout extended timeframes by conducting long-term studies. Medical study should explore therapeutic combinations which merge hydroxyurea with current treatment approaches to maximize treatment success. Gene-editing method advances will enhance curative procedures by making them more available and affordable for a wider demographic of patients with SCD.

## Abbreviation

1. **SCD** – Sickle Cell Disease
2. **HbS** – Hemoglobin S
3. **VOC** – Vaso-Occlusive Crisis
4. **HbF** – Fetal Hemoglobin
5. **LDH** – Lactate Dehydrogenase
6. **SPSS** – Statistical Package for the Social Sciences
7. **SD** – Standard Deviation
8. **ANOVA** – Analysis of Variance

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## Authors Contribution

Concept & Design of Study: Adnan Masood[1]

Drafting: Adnan Masood[1]

Data Analysis: Adnan Masood[1]

Critical Review: Adnan Masood[1]

Final Approval of version: Adnan Masood[1]

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