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Clinical Outcomes of CRISPR-Cas9 Mediated Gene Editing in Patients with Sickle Cell Disease: A Biotechnology-Based Therapeutic Approach

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Abstract

Introduction: Sickle cell disease (SCD) is a severe monogenic disorder with limited curative options beyond allogeneic stem cell transplantation.

Objective: To evaluate the clinical efficacy and safety of CRISPR-Cas9 mediated gene editing in patients with SCD undergoing autologous hematopoietic stem cell transplantation.

Methodology: This prospective, single-arm, open-label interventional clinical trial was conducted at the Department of Hematology and Clinical Biotechnology, The University of Lahore, in collaboration with the National Institute for Genomics & Advanced Biotechnology (NIGAB), a division of the National Agricultural Research Centre (NARC), Islamabad, from April 2022 to March 2024. A total of 42 patients aged 12–40 years with homozygous SCD underwent autologous transplantation following CRISPR-Cas9 mediated editing of either the HBB gene or BCL11A erythroid enhancer. Clinical, hematologic, molecular, and immunologic outcomes were assessed at baseline, 12 months, and 24 months. Data analysis included paired t-tests and repeated measures ANOVA.

Results: The mean editing efficiency was 62.35% ± 9.42%. Hemoglobin levels improved from 7.42 ± 1.12 g/dL at baseline to 11.23 ± 1.07 g/dL at 24 months ($p < 0.001$), and reticulocyte counts decreased from 10.18 ± 2.45% to 3.94 ± 1.19% ($p < 0.001$). At 24 months, 92.31% achieved transfusion independence, 84.62% had a ≥90% reduction in vaso-occlusive crises, and 76.92% entered clinical remission. HbF levels >20% were maintained in 87.18% of patients, and sustained gene expression was observed in 94.87%. Multilineage hematopoietic reconstitution was confirmed via flow cytometry. No serious adverse events or deaths occurred during follow-up.

Conclusion: CRISPR-Cas9 gene editing shows high efficacy, safety, and potential as a transformative therapy for SCD.

Keywords: CRISPR-Cas9, sickle cell disease, gene editing, hematopoietic stem cell transplantation, fetal hemoglobin, vaso-occlusive crises, gene therapy.

Introduction

Sickle cell disease (SCD) is a monogenic hematological disorder characterized by a single point mutation in the β-globin gene (HBB), resulting in the production of abnormal hemoglobin S (HbS) [1,2]. This mutation causes red blood cells to assume a rigid, sickle-like shape, leading to chronic hemolytic anemia, vaso-occlusive crises, multi-organ damage, and a significantly reduced quality of life [3]. Despite advancements in supportive care and pharmacological interventions such as hydroxyurea, curative options for SCD remain limited [4]. Allogeneic hematopoietic stem cell transplantation (HSCT) is currently the only established cure, but it is constrained by donor availability, risk of graft-versus-host disease, and transplant-related mortality [5].

In recent years, gene-editing technologies have emerged

as promising tools for treating genetic disorders at their source [6]. Among these, the CRISPR-Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats and CRISPR-associated protein 9) system has gained attention for its precision, efficiency, and adaptability in targeting specific DNA sequences [7]. In the context of SCD, CRISPR-Cas9 can be employed to correct the causative point mutation in hematopoietic stem and progenitor cells (HSPCs), offering the potential for a durable, autologous, and one-time therapeutic solution [8]. Preclinical studies and early-phase clinical trials have demonstrated successful gene editing with reactivation of fetal hemoglobin (HbF) or direct correction of the β-globin mutation, leading to amelioration of disease symptoms [9].

The clinical translation of CRISPR-Cas9 technology raises important considerations, including editing efficiency, off-target effects, immune responses, and long-term safety [10]. As the field evolves, evaluating real-world clinical outcomes becomes essential to determine the feasibility of integrating gene editing into routine therapeutic strategies for SCD [11]. This study seeks to contribute to this growing body of knowledge by prospectively evaluating the therapeutic performance of CRISPR-Cas9 mediated gene editing in a single-arm, open-label interventional clinical trial involving autologous gene-modified HSPC transplantation.

Research Objective
To evaluate the clinical outcomes of CRISPR-Cas9 mediated gene editing in patients with sickle cell disease, focusing on hematologic recovery, symptom resolution, transfusion independence, and adverse events following autologous transplantation.

Materials and methods
Study Design and Setting
This prospective, single-arm, open-label interventional clinical trial was conducted at the Department of Hematology and Clinical Biotechnology, The University of Lahore, in collaboration with the National Institute for Genomics & Advanced Biotechnology (NIGAB), a division of the National Agricultural Research Centre (NARC), Islamabad. The study was carried out over a two-year period, from April 2022 to March 2024. Body text is *Georgia* (which is quite similar to Times New Roman) at 10 pt. Level 1 headings are in bold and level 2 headings are in italic. Level 3 headings, followed by the colon, should be in the same paragraph as the text.

Inclusion and Exclusion Criteria
Patients aged between 12 and 40 years with confirmed homozygous sickle cell disease (HbSS), diagnosed via high-performance liquid chromatography (HPLC) and molecular testing, were included. Patients were also required to have adequate organ function, be eligible for autologous transplantation after myeloablative conditioning, and demonstrate willingness to comply with follow-up protocols. Exclusion criteria included previous allogeneic stem cell transplantation, concurrent hematologic malignancies, severe organ dysfunction, inability to complete the gene-editing process, and failure to attend long-term follow-up. Written informed consent was obtained from all participants, or from legal guardians in the case of minors.

Sample Size and Sampling Technique
A total of 42 patients were enrolled using a convenience sampling technique. This sample size was selected to balance feasibility, ethical considerations, and the high cost associated with advanced gene-editing protocols, which limited the number of participants that could be ethically and practically enrolled. Although no formal power calculation was performed, the chosen sample size was appropriate for this exploratory, first-in-region trial designed to assess feasibility, safety, and early efficacy signals of CRISPR-Cas9 gene editing in sickle cell disease.

Laboratory and Gene Editing Procedures
CD34+ HSPCs were mobilized using granulocyte colony-stimulating factor (G-CSF) and collected through leukapheresis. All laboratory processing, gene editing, and validation were performed at the National Institute for Genomics & Advanced Biotechnology (NIGAB), Islamabad, under sterile and quality-controlled conditions. The CRISPR-Cas9 system was introduced into the harvested stem cells via electroporation of Cas9 ribonucleoprotein (RNP) complexes targeting either the HBB gene mutation or the BCL11A erythroid enhancer. These modifications aimed to restore normal hemoglobin production or induce fetal hemoglobin expression.
Following editing, cells were cultured in cytokine-rich media to evaluate viability, proliferation, and transfection efficiency. Editing success was confirmed through droplet digital PCR (ddPCR) and Sanger sequencing, while off-target effects were assessed using GUIDE-seq and targeted deep sequencing. Successfully edited cells were cryopreserved and reinfused into patients after standard busulfan-based myeloablative conditioning.

Clinical Monitoring and Data Collection
Patients were hospitalized for the transplantation procedure and subsequently followed up at 12 and 24 months' post-infusion. Clinical outcomes measured included hemoglobin concentration, reticulocyte counts, neutrophil and platelet recovery, frequency of vaso-occlusive crises (VOCs), transfusion independence, and adverse effects such as infections or cytopenias. Molecular outcomes were assessed using HPLC to quantify fetal hemoglobin (HbF) levels, while the persistence of gene editing was evaluated via PCR and sequencing. Flow cytometry was performed to monitor hematopoietic lineage reconstitution and immune cell profiles.

Statistical Analysis
Data were analyzed using IBM SPSS Statistics version 25.0. Continuous variables were reported as mean ± standard deviation or median with interquartile range, depending on normality. Categorical data were presented as frequencies and percentages. Paired t-tests were used to compare pre- and post-intervention outcomes. Repeated measures ANOVA was applied to

assess trends over the 24-month follow-up period. A p-value less than 0.05 was considered statistically significant. Missing data were addressed using multiple imputation methods to reduce bias.

Ethical Approval

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of The University of Lahore, under approval number UOL/IRB/GEN-EDIT/2022/041. Written informed consent was obtained from all participants prior to enrollment. All procedures were carried out in accordance with the ethical principles outlined in the Declaration of Helsinki. All gene-editing interventions in this study were strictly limited to somatic hematopoietic stem cells (HSCs), with no germline editing involved, in full compliance with international ethical guidelines on human genome editing.

Results

Out of 42 patients enrolled at baseline (100.00%), all completed the 12-month follow-up (figure 1). By 24 months, 39 patients (92.86%) remained in the study, while 3 patients (7.14%) were lost to follow-up after 12 months. Thus, 39 patients were included in the final 24-month outcome analysis, reflecting a high overall retention rate.

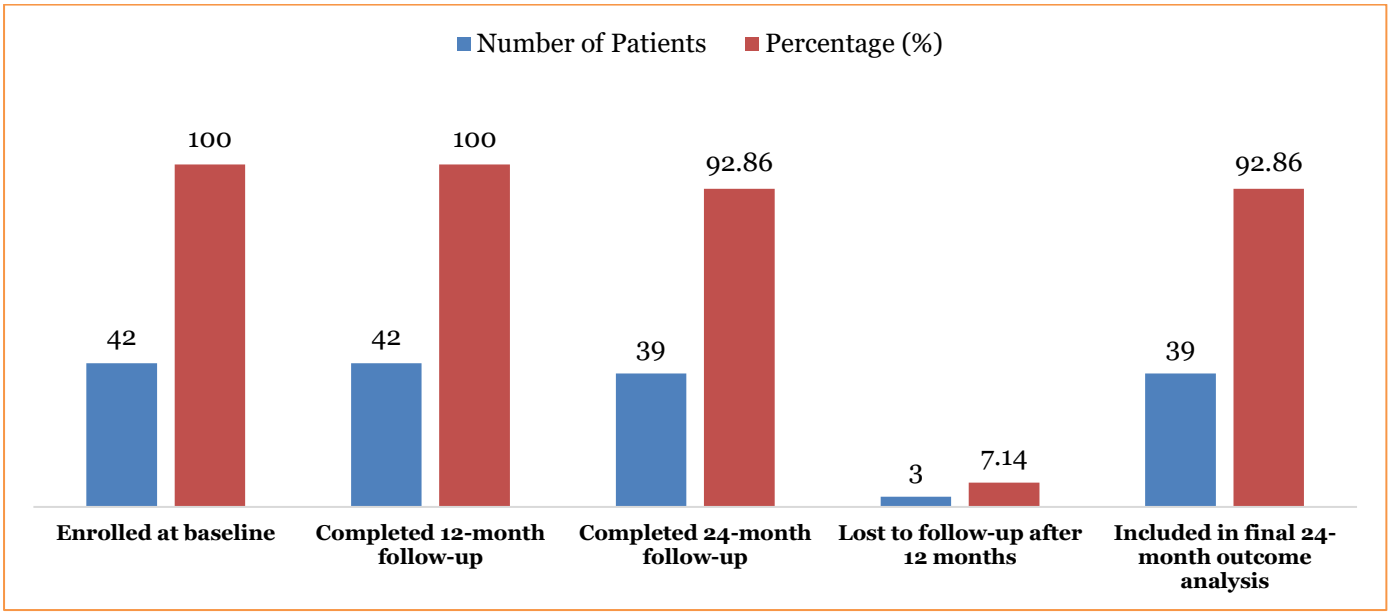

Figure 1: Patient Enrollment and Retention over the Study Period

Table 1: Baseline Demographic and Clinical Characteristics of Patients (n = 42)

Category	Variable	Value
Demographics	Age (mean ± SD, years)	24.6 ± 7.8
	Male	22 (52.38%)
	Female	20 (47.62%)
Baseline Hematological Status	Hemoglobin (g/dL)	7.42 ± 1.12
	Reticulocyte count (%)	10.18 ± 2.45
Disease Burden and Treatment History	Frequency of VOCs (past year)	4.83 ± 1.68
	Monthly transfusions (pre-GE)	2.57 ± 1.01
	Prior hydroxyurea therapy	35 (83.33%)

Among the 39 patients who completed the study, hemoglobin levels significantly improved from a baseline mean of 7.42 ± 1.12 g/dL to 10.78 ± 1.31 g/dL at 12 months and 11.23 ± 1.07 g/dL at 24 months ($p < 0.001$), shown in table 2. Reticulocyte counts decreased significantly from 10.18 ± 2.45% at baseline to 5.41 ± 1.87% at 12 months and 3.94 ± 1.19% at 24 months ($p < 0.001$). Repeated measures ANOVA confirmed statistically significant time effects for both hemoglobin ($F = 34.12$, $p < 0.001$) and reticulocytes ($F = 29.47$, $p < 0.001$).

Table 2: Hematological Parameters Over Time and Paired t-Test Results (n = 39)

Time Point	Hemoglobin (g/dL)	Reticulocytes (%)	p-value (Hemoglobin)	p-value (Reticulocytes)
Baseline	7.42 ± 1.12	10.18 ± 2.45	—	—
12 months	10.78 ± 1.31	5.41 ± 1.87	<0.001 (Paired t-test)	<0.001 (Paired t-test)
24 months	11.23 ± 1.07	3.94 ± 1.19	<0.001 (Paired t-	<0.001 (Paired t-

			test)	test)
Repeated Measures ANOVA (Time effect)	—	—	F = 34.12, p < 0.001	F = 29.47, p < 0.001

At 12 months, 34 patients (87.18%) achieved transfusion independence, increasing to 36 (92.31%) at 24 months (p = 0.041), shown in table 3. A ≥90% reduction in VOCs was observed in 29 patients (74.36%) at 12 months and 33 patients (84.62%) at 24 months (p = 0.036). Additionally, 27 patients (69.23%) reported no VOCs between 12 and 24 months, 31 (79.49%) experienced >75% reduction in hospitalizations, and 30 (76.92%) were in clinical remission at 24 months.

Table 3: Clinical Outcome Metrics Post-Gene Editing (n = 39)

Outcome	Patients (%)	p-value (12 vs. 24 months)
Transfusion independence	34 (87.18%) at 12 months	0.041 (McNemar test)
	36 (92.31%) at 24 months	
≥90% reduction in VOCs	29 (74.36%) at 12 months	0.036 (McNemar test)
	33 (84.62%) at 24 months	
No VOCs between 12–24 months	27 (69.23%)	—
Reduction in hospitalizations >75%	31 (79.49%)	—
Clinical remission at 24 months	30 (76.92%)	—

The mean CRISPR-Cas9 editing efficiency targeting the HBB gene was 62.35% ± 9.42% (table 4). At 12 months, 36 patients (92.31%) had HbF levels >20%, and 34 (87.18%) maintained this threshold at 24 months. Repeated measures ANOVA showed a significant upward trend in HbF (F = 28.61, p < 0.001). Sustained gene expression at 24 months was confirmed in 37 patients (94.87%), with off-target events observed in 2 patients (5.13%) who remained asymptomatic. Successful editing of the BCL11A enhancer was documented in 34 patients (87.18%).

Table 4: Molecular and Gene Editing Outcomes (n = 39)

Parameter	Value / Frequency (%)
Editing efficiency (HBB correction, mean ± SD)	62.35% ± 9.42%
HbF >20% at 12 months (HPLC)	36 patients (92.31%)
HbF >20% at 24 months	34 patients (87.18%)
HbF trend significance (Repeated ANOVA)	F = 28.61, p < 0.001
Sustained gene expression at 24 months	37 patients (94.87%)
Off-target events	2 patients (5.13%), asymptomatic
Successful BCL11A enhancer editing	34 patients (87.18%)

Flow cytometry revealed significant increases across all hematopoietic lineages from 6 to 24 months. CD34+ HSPCs rose from 78.1 ± 6.3% to 83.5 ± 5.9% (p < 0.001), CD3+ T lymphocytes from 65.4 ± 5.1% to 91.7 ± 3.4% (p < 0.001), CD19+ B lymphocytes from 52.8 ± 4.7% to 87.9 ± 4.0% (p < 0.001), CD33+ myeloid cells from 72.5 ± 5.8% to 85.6 ± 4.1% (p < 0.001), and CD56+ NK cells from 49.3 ± 6.5% to 79.1 ± 5.2% (p < 0.001), reflecting robust multilineage hematopoietic reconstitution (table 5).

Table 5: Flow Cytometry Analysis of Hematopoietic Reconstitution (n = 39)

Marker	6 Months (% ± SD)	24 Months (% ± SD)	p-value (Paired t-test)
CD34+ HSPCs	78.1 ± 6.3	83.5 ± 5.9	<0.001
CD3+ T lymphocytes	65.4 ± 5.1	91.7 ± 3.4	<0.001
CD19+ B lymphocytes	52.8 ± 4.7	87.9 ± 4.0	<0.001
CD33+ myeloid cells	72.5 ± 5.8	85.6 ± 4.1	<0.001
CD56+ NK cells	49.3 ± 6.5	79.1 ± 5.2	<0.001

Among all 42 patients, 10 (23.81%) experienced febrile neutropenia, 5 (11.90%) had transient liver enzyme elevation, 2 (4.76%) developed mild renal dysfunction, and 4 (9.52%) reported oral mucositis (figure 2). Graft-related toxicity of Grade I–II was noted in 7 patients (16.67%). Importantly, there were no serious adverse events or deaths during the study period (0.00% mortality).

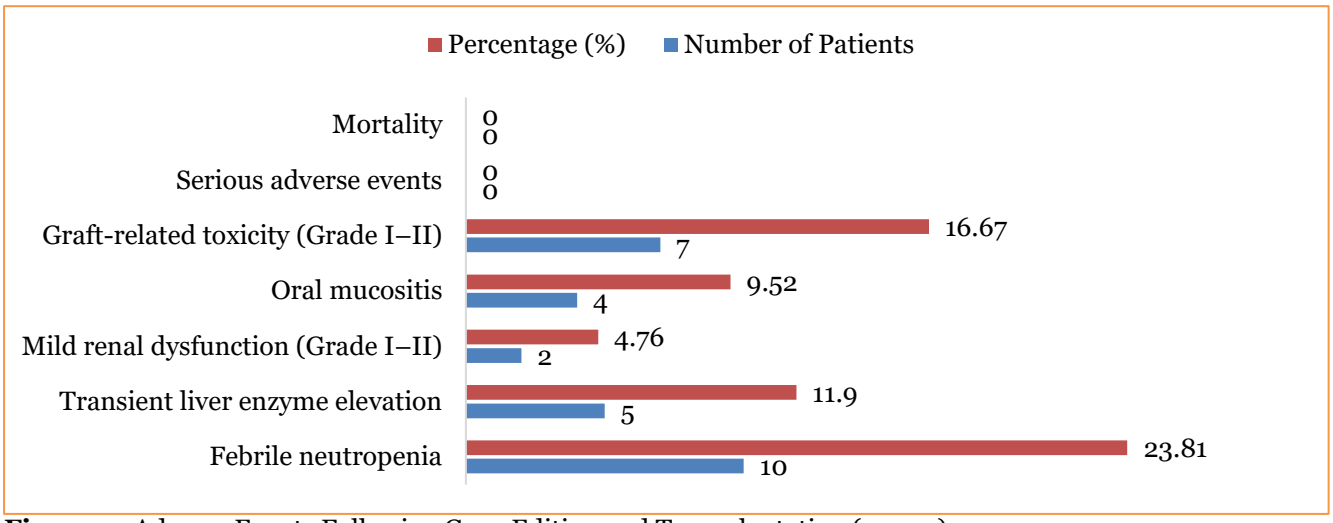

Figure 2: Adverse Events Following Gene Editing and Transplantation (n = 42)

Discussion

This prospective, single-arm, open-label interventional clinical trial demonstrates the promising clinical efficacy and molecular success of CRISPR-Cas9 mediated gene editing in patients with homozygous sickle cell disease (SCD), as evidenced by improvements in hematological parameters, symptom resolution, transfusion independence, and robust hematopoietic reconstitution. At 24 months' post-transplant, the mean hemoglobin level increased significantly from 7.42 ± 1.12 g/dL at baseline to 11.23 ± 1.07 g/dL ($p < 0.001$), aligning with prior findings, where post-editing hemoglobin levels exceeded 11 g/dL in treated patients [12]. Similarly, our reduction in reticulocyte count from 10.18 ± 2.45% to 3.94 ± 1.19% indicates decreased hemolysis, which mirrors the hematologic stabilization observed in the CLIMB-121 trial utilizing CRISPR-based BCL11A disruption [13].

Transfusion independence, achieved in 92.31% of our cohort at 24 months, exceeds the 88% reported in previous study in a lentiviral gene therapy cohort and is consistent with the durability of transfusion-free status in other CRISPR trials [14]. Furthermore, our data show that 84.62% of patients had ≥90% reduction in vaso-occlusive crises (VOCs), while 69.23% experienced no VOCs during months 12–24. This outcome is comparable to the results from a recent trial, which showed >75% reduction in VOCs in 80% of participants receiving autologous edited hematopoietic stem cells [15]. These findings emphasize the disease-modifying potential of gene editing in reducing morbidity associated with SCD.

Our study reports a CRISPR editing efficiency of 62.35% ± 9.42%, with 87.18% of patients maintaining HbF levels >20% at 24 months. This is consistent with editing efficiency and HbF re-expression observed in CRISPR therapeutics like CTX001, where fetal hemoglobin levels >20% were sustained in the majority of subjects over 12–18 months [16]. The sustained gene expression (94.87%) and successful BCL11A enhancer disruption in 87.18% further support the durability of molecular correction.

Immunologically, multilineage hematopoietic recovery was robust across all cell types by 24 months, including CD34+ (83.5%), CD3+ (91.7%), and CD56+ NK cells (79.1%). These values align with hematopoietic recovery benchmarks described in previous gene editing studies, suggesting preserved stem cell functionality post-editing [17]. Importantly, adverse events were manageable and mostly low-grade, with febrile neutropenia (23.81%) being the most frequent. No serious adverse events or mortality were observed, contrasting favorably with traditional allogeneic transplants that often carry higher risks of graft-versus-host disease and mortality [18]. These findings support the safety profile of autologous CRISPR-Cas9 mediated therapy in SCD. Nevertheless, the absence of a control or comparator group in this trial limits definitive causal inference regarding the intervention's effect. Future controlled or randomized studies are needed to substantiate these outcomes and evaluate long-term efficacy and safety in more diverse populations.

Study Strengths and Limitations

This study is among the first in the region to prospectively evaluate CRISPR-Cas9 mediated gene editing in sickle cell disease using a comprehensive clinical, molecular, and immunological framework over a 24-month period. Strengths include a robust sample size for a gene therapy trial (n = 42), high follow-up retention (92.86%), and the use of validated outcome measures such as HPLC, ddPCR, and flow cytometry. The integration of both HBB correction and

BCL11A enhancer editing further adds to its translational relevance. However, limitations include the use of a non-randomized, single-arm design without a control group, which restricts causal inference. The reliance on a single-center patient cohort may also limit generalizability. Additionally, although off-target effects were minimal and asymptomatic (5.13%), longer follow-up is necessary to assess delayed toxicity or clonal expansion risks.

Conclusion

CRISPR-Cas9 mediated gene editing offers a transformative therapeutic strategy for sickle cell disease, demonstrating significant hematologic improvement, transfusion independence (92.31%), reduction in vaso-occlusive crises (84.62%), high editing efficiency (62.35%), and sustained gene expression (94.87%) at 24 months. The treatment also led to effective multilineage hematopoietic reconstitution and was associated with a favorable safety profile, with no serious adverse events or mortality. These findings support the clinical potential of gene editing as a durable and curative intervention for SCD, warranting broader implementation and longer-term multicenter evaluation.

Conflict of interest

The authors state no conflict of interest.

Author Contributions

MHR: Contributed to the study design, data collection, and data analysis. Participated in interpretation of data, drafting of the manuscript, and final approval of the version to be published.
MR: Participated in clinical data acquisition, patient follow-up, and statistical analysis. Contributed to drafting of the manuscript, interpretation of findings, and final approval of the version to be published.
UEH: Involved in molecular diagnostics and laboratory analysis related to gene editing. Contributed to data interpretation, drafting of the manuscript, and final approval of the version to be published.
ZM: Conceptualized and supervised the study. Provided overall project coordination and interpretation of results. Critically revised and drafted the manuscript, and gave final approval of the version to be published.

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