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Research Article

Efficacy and safety of lentivirus gene therapy in the correction of sickle cell disease

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Abstract

***Background and objective**:* Lentivirus gene therapy (LGT) is an emerging therapy for sickle cell disease (SCD), although its efficacy and safety are under evaluation in clinical trials. This review assessed the efficacy and safety of LGT in relation to hydroxyurea (HU).

***Materials and methods**:* A systematic review was conducted using The Preferred Reporting Items for Systematic Review and Meta-analysis protocol. Following a set of inclusion criteria, 10 studies were selected for quality assessment, extraction, and meta-analysis from 499 studies pooled from PubMed, ScienceDirect and Sematic Scholar. Data obtained were described and subjected to random effect meta-analysis using RevMan software.

***Results**:* There was a significant increase (p-value<0.00001) in haemoglobin (Hb) level after LGT and production of HbAT87Q and foetal haemoglobin (HbF). Clinical outcome decreased significantly, and no hospitalization was required following LGT. A significant age-related difference in the LGT outcome was observed. Mode 1 treatment had significantly higher (p=0.004) outcome compared to mode 2 treatment. There was a significant increase (p<0.00001) in treatment outcome in SCD patients treated with LGT compared to those treated with HU. Gastroenteritis and leucopenia were the most reported adverse effects.

***Conclusion**:* The review has demonstrated that LGT has a promising efficacy in the treatment of SCD although there are existing safety concerns.

Introduction

Sickle cell disease (SCD) comprises a set of hereditary blood disorders impacting the structure and function of red blood cells (RBCs) [1-3]. These cells, which typically transport oxygen throughout the body, undergo a transformation in SCD, adopting a rigid and sickle-shaped form. This alteration gives rise to a range of complications, including anemia, pain, infections, organ damage, and stroke [4]. The root cause of SCD lies in a genetic mutation affecting the hemoglobin-coding gene, leading to the synthesis of abnormal hemoglobin, termed hemoglobin S. This variant hemoglobin S, polymerizes under low oxygen conditions, distorting the shape of RBCs [5].

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The pathophysiology of SCD is intricate, involving several factors, such as hemolysis, vaso-occlusion, inflammation, oxidative stress, endothelial dysfunction, and hypercoagulability [6-8]. Treatment of SCD aims to prevent or mitigate the frequency and severity of complications, enhance quality of life, and extend lifespan of the patient. Existing therapeutic approaches encompass supportive care, pharmacological agents, and hematopoietic stem cell transplantation (HSCT) [9,10]. Various supportive care approaches include hydration, analgesics and antibiotics administration, blood transfusions, and immunization modalities [11,12]. Among pharmacological agents, hydroxyurea stands out—an agent boosting fetal hemoglobin production, thereby reducing the polymerization of hemoglobin S and the sickling of RBCs [12]. Demonstrating efficacy, hydroxyurea has been linked to a decrease in pain crises, incidents of acute chest syndrome, hospitalizations, and increased mortality rate in SCD patients [13]. Nevertheless, challenges such as variable response, adverse effects, and compliance issues temper its utility [14].

For those seeking a curative option, hematopoietic stem cell transplantation (HSCT) emerges as a transformative approach. This process entails replacing the defective hematopoietic stem cells (HSCs) of the patient with healthy HSCs from a compatible donor, restoring normal hemoglobin production and eliminating the manifestations of SCD [9]. However, HSCT includes adverse effects such as graft-versus-host disease, graft failure, infections, and infertility [9]. Furthermore, its applicability is constrained by the availability of suitable donors and the high cost associated with the procedure [9,15].

At present, a cutting-edge alternative in SCD intervention is gene therapy, aiming to rectify the underlying genetic anomaly at its source. This innovative approach involves the introduction of a functional gene into specific target cells, notably hematopoietic stem cells (HSCs), to bring about modifications in their gene expression and phenotype character [16]. Gene therapies broadly fall into two categories: gene addition and gene editing. Gene addition involves incorporating a therapeutic gene into the genome of the target cells without altering existing genes [16]. On the other hand, gene editing entails the precise modification or correction of the target gene, employing advanced tools such as zinc finger nucleases, transcription activator-like effector nucleases, or the CRISPR-Cas9 system [17,18]. One of the most exciting advances in sickle cell disease (SCD) treatment is the use of CRISPR/Cas9 gene editing, a technology that allows scientists to make precise changes to DNA. Generally, CRISPR is palindromic sequence in bacterial genome which can be excised by the cas9 enzyme, allowing scientists to modify, edit, insert or delete genes according to convenience. This breakthrough has led to CASGEVY™ (exagamglo gene autotemcel, or exa-cel), the first FDA-approved CRISPR-based therapy for SCD, developed by Vertex Pharmaceuticals and CRISPR Therapeutics. CASGEVY works by editing a patient's own stem cells to boost the production of fetal hemoglobin (HbF), which helps counteract the harmful effects of sickle hemoglobin [19,20]. The FDA approval of CASGEVY in late 2023 was a landmark moment not just for SCD patients, but for the entire field of gene therapy. For decades, researchers have been working toward a true cure for SCD, and this therapy represents a major step forward. Clinical trials have shown that CASGEVY can dramatically reduce or even eliminate pain crises in many patients, offering hope for a life free from the most debilitating symptoms of SCD [21]. Beyond its clinical success, CASGEVY's approval also sets a precedent for future gene-editing treatments, proving that CRISPR technology can be both safe and effective in treating genetic disorders. While challenges like cost and accessibility remain, this therapy opens a new era of personalized medicine for SCD patients [22,23].

Lentivirus gene therapy (LGT) represents a subtype of gene addition therapy utilizing lentiviruses as vectors to transport the therapeutic gene into the targeted cells. Lentiviruses, belonging to the retrovirus family, possess the unique capability to infect both dividing and non-dividing cells, integrating their genetic material seamlessly into the host genome [15]. LGT offers several advantages over alternative gene therapy vectors, including high transduction efficacy, stable gene expression, low immunogenicity, and a large transgene capacity [24]

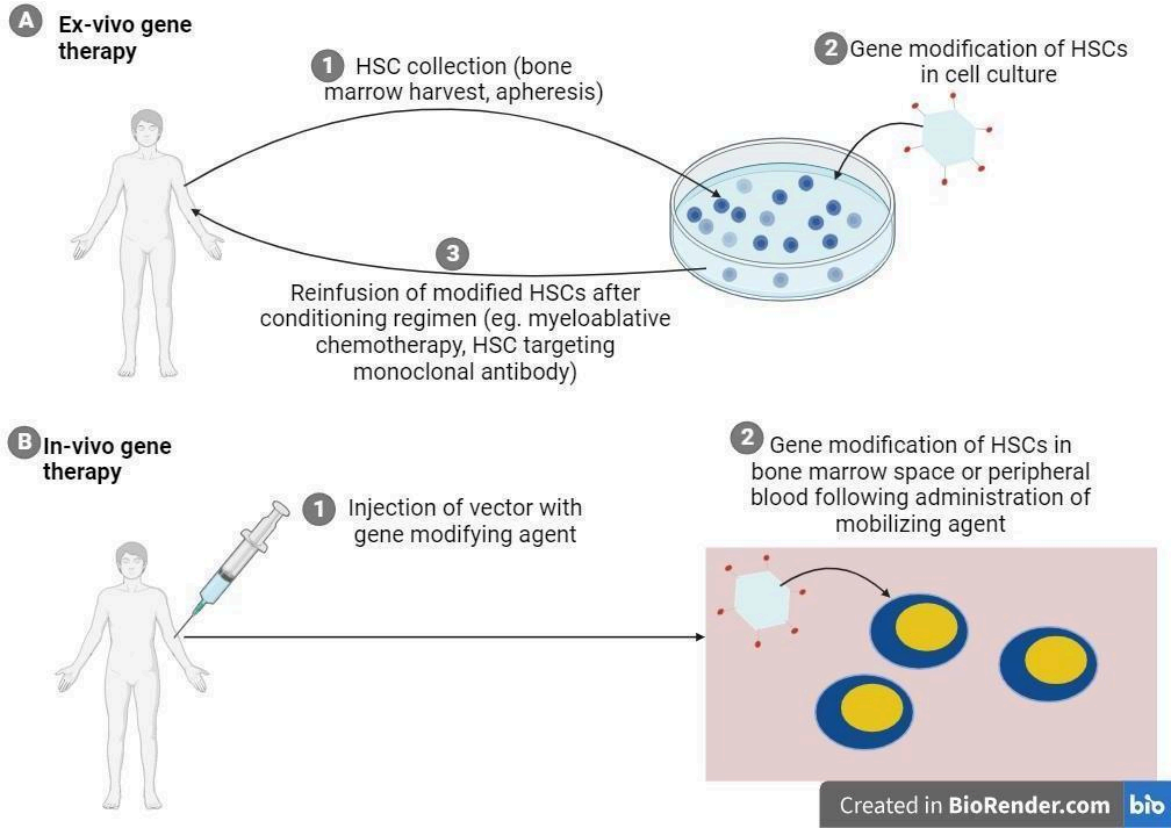

Figure-1: *General Schema for Gene Therapy [25]*
(A) Ex Vivo Therapy: Hematopoietic stem cells (HSCs) are collected, modified externally (introducing or editing genes), and reinfused to address genetic defects at their source.
(B) In Vivo Gene Therapy: Systemic delivery of a gene-modifying agent with affinity for HSCs directly targets cells within the patient's body, providing a streamlined and less invasive gene therapy approach.

The efficacy of LGT hinges on the type of therapeutic gene delivered by the lentiviral vector [29]. In the context of sickle cell disease (SCD), there are two primary strategies for LGT: anti-sickling gene therapy and globin gene therapy [16,25-34]. Anti-sickling gene therapy entails the delivery of a gene encoding a modified hemoglobin variant capable of preventing or reducing the polymerization and sickling of hemoglobin S [32-34]. Examples of anti-sickling genes include hemoglobin F (HbF), the fetal form of hemoglobin typically silenced after birth, and hemoglobin A (HbA), the normal adult form of hemoglobin mutated in SCD [32-34]. Other examples involve hemoglobin A2 (HbA2), a minor adult hemoglobin form, and hemoglobin mutants like hemoglobin E (HbE) and hemoglobin G (HbG), both possessing reduced affinity for hemoglobin S [32-35].

Globin gene therapy, on the other hand, involves delivering a gene encoding a functional globin chain, such as beta-globin or gamma-globin, to restore the balance and production of globin chains in SCD [34,36,37]. SCD is characterized by a deficiency of beta-globin, leading to an excess of alpha-globin, resulting in ineffective erythropoiesis and hemolysis [38]. By introducing a functional beta-globin or gamma-globin gene, LGT can increase the synthesis of hemoglobin A or hemoglobin F, respectively, correcting the alpha-beta globin imbalance [37,38].

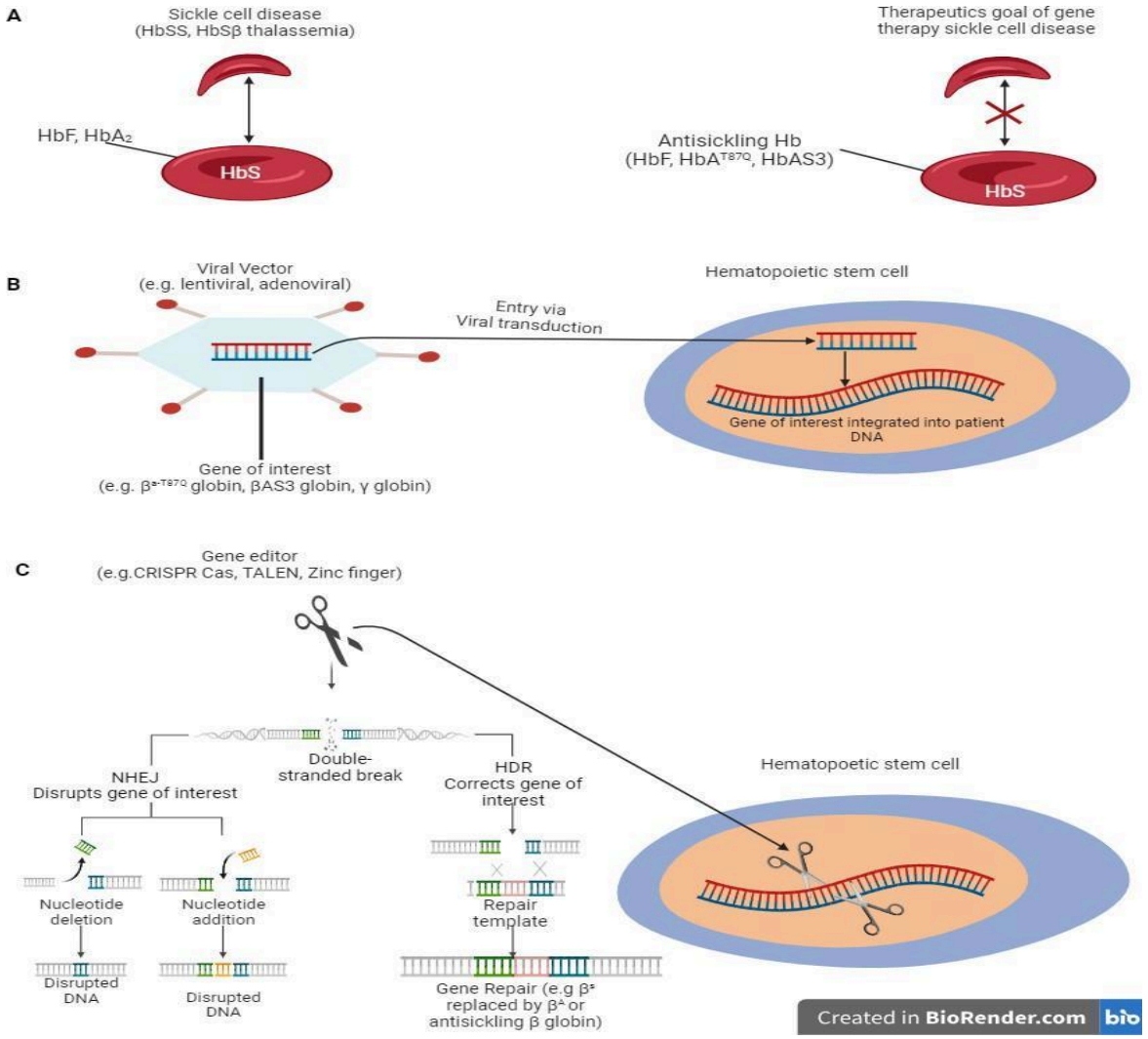

Figure-2: *Gene therapy strategies for SCD. (A) Antisickling globin expression as a gene-therapy strategy to prevent RBC sickling. (B) Gene-addition strategy to deliver antisickling genes. (C) Gene-editing approaches to induce HbF by NHEJ and gene repair by HDR.*
Abbreviations: HDR – Homology Direct Repair, SCD -Sickle cell disease, HbF –Foetal Haemoglobin, NHEJ – Non -Homologous end joining, RBC- Red blood cell.

Ensuring the safety of LGT requires careful consideration of potential challenges such as insertional mutagenesis, immune responses, off-target effects, adverse events, immunosuppression, hematologic parameters, reproductive markers, and vigilant monitoring for clonal dominance. Mitigation strategies encompass the utilization of self-inactivating vectors, administering low vector doses, employing autologous cells, utilizing high-fidelity vectors, incorporating immunosuppressive drugs, and employing advanced monitoring techniques [39-41].

To gauge the effectiveness of this therapeutic approach, a range of assessment methods is employed. In vitro analyses are conducted to

scrutinize alterations in vector titers and transduction efficacy [42]. In vivo studies entail the transplantation of vector- or mock-transduced cells into animal models to evaluate therapeutic effectiveness [42]. Rigorous clinical trials are undertaken to assess the safety and efficacy of the lentiviral vector, the in vivo gene transfer clinical protocol, and the sustained correction of associated pathological symptoms [43]. The evaluation of vector integration sites is crucial to ensure the safety of the gene therapy [43]. Additionally, measuring degradative metabolite levels in patients during treatment aids in evaluating therapeutic efficacy [43]. The monitoring of clinical endpoints involves observing changes in disease symptoms, the frequency of disease-related complications, and the overall health and quality of life of patients [44]. These outcomes aim to improve oxygen-carrying capacity, minimize painful episodes, prevent life-threatening complications, and enhance the overall well-being of individuals with SCD.

Exploration of LGT for SCD has been documented in studies such as those conducted by creative biolabs and Walters et al. [45,46]. These investigations have effectively demonstrated the safety and efficacy of LGT, showcasing stable engraftment, elevated hemoglobin levels, and substantial improvement in SCD symptoms without encountering adverse events or complications. Significantly, these studies have contributed groundbreaking clinical evidence, suggesting the potential for LGT to serve as a gene therapy cure for SCD. This underscores the viability of LGT utilizing various beta- and gamma-globin genes.

While LGT has shown promising outcomes, it is essential to acknowledge certain limitations that warrant attention. These limitations are limited patient numbers, short follow-up periods, and a deficiency in long-term data [47]. To strengthen the robustness of LGT's safety and efficacy profile, further studies are imperative. These studies should delve into critical parameters such as lentiviral vector design, conditioning regimens, transduction protocols, and comparative analyses with alternative gene therapy strategies [47]. Additionally, the optimization of clinical endpoints and the resolution of practical challenges, including cost, accessibility, ethics, and regulation, are pivotal for propelling LGT toward becoming a viable treatment for Sickle Cell Disease [47].

Conducting a comprehensive review of lentivirus gene therapy for SCD is undeniably crucial. Existing treatments for SCD often lack a definitive cure, with variable effectiveness among patients. Lentivirus gene therapy, in contrast, has shown promising results in treating SCD and holds the potential for a curative approach [48]. Nevertheless, a thorough understanding of the safety and efficacy of this therapy remains a priority. By scrutinizing the existing literature on lentivirus gene therapy for SCD, identifying knowledge gaps, and shaping future research directions, we can contribute to the development of more effective and potentially curative treatments for SCD.

Materials and methods

The Preferred Reporting Items for Systematic Review and Meta-analysis (PRIMSA) protocol of 2015 [49] was followed in the step-by-step development of the review to ensure reproducibility and transparency in the review process. The summary of the PRISMA protocol was reported using a PRISMA flowchart.

Study selection criteria: inclusion criteria: Studies included were clinical trials reporting the efficacy of LGT in correcting gene mutation in SCD in human subjects. Also included were studies focusing on safety and adverse effects of LGT in the treatment of SCD patients. Studies also considering the efficacy and safety of hydroxyurea (HU) for SCD treatment were equally considered. Overall, studies included were original articles from peer-reviewed journals from relevant repositories or online databases.

Exclusion criteria: Studies not relevant to LGT in SCD such as other haemoglobinopathies like thalassemia were excluded. Animal studies, editorials and review articles, original studies using other forms of gene therapy were also excluded.

Information Sources-The following electronic databases or repositories used for the systematic review are as follows: PubMed, ScienceDirect and Semantic scholar.

Search strategy: A comprehensive search strategy was developed using a combination of Boolean function [50] and filters to narrow the study to original articles and clinical trials (randomized and non-randomized clinical trials) with advanced search including specific keywords like “lentivirus sickle cell disease” particularly for ScienceDirect. It is important to mention that the search strategy was adjusted to the specific provisions of each database.

Table-1: *Search Query/Boolean Function*

Database	Search query/Boolean function
PubMed	("Lentivirus gene therapy" OR "gene therapy") AND ("sickle cell disease" OR "sickle cell anemia") AND ("effectiveness" OR "efficacy" OR "safety" OR "adverse effects" OR "side effects" OR "hydroxyurea" OR "stem cell transplantation")
ScienceDirect	efficacy and safety of lentivirus gene therapy in sickle cell anaemia "lentivirus""sickle cell disease"
Semantic scholar	efficacy OR effectiveness AND safety AND lentivirus gene AND therapy AND ase

Data management: All search results from the listed databases were first imported and managed by EndNote software, after which they were exported as XML files to Covidence for screening, selection, extraction and quality assessment of the included studies. Leveraging on the features of the software (EndNote), streamlining the process of reference formatting of included studies to the desired citation style was possible [51]. Covidence is a web-based tool for systematic review management [52,53] following PRISMA guideline, including title and abstract screening, full text screening, quality assessment. The Covidence tool was also used for data extraction and PRISMA flowchart generation [52,53].

Study selection and data extraction: Screening of titles and abstracts was done separately to find studies that might be suitable for full review. Then, the full texts of those studies were checked based on specific criteria. Studies that met these criteria were selected for data collection. The data collected included the study type, patient details, type and dose of treatment, lab results, clinical results, and, if needed, information on side effects.

Quality assessment: Virtually all the studies included were in the 1/2 phase of clinical trial. Since these phases of studies are typical of pilot studies, the checklist tool used was put into consideration to capture the peculiarity of such studies because studies in early phase clinical trials may require modifications in their quality assessment due to their uniqueness. In this case the studies were neither a full-scale clinical nor randomized clinical trial. To fulfill this purpose, the University of Chicago checklist for pilot studies was used to judge the quality of each study. It reflected at parameters such as the study’s goal, the reason for doing it, whether the way data was collected matched the goal, the number of participants (though not in a strict statistical way), if the data collection method would work in a larger study, and whether there was a good reason to move forward with a full-scale study.[54].

Data synthesis and analysis: Qualitatively, a narrative synthesis of studies included was described with provision of the overview of the evidence. Furthermore, meta-analysis was carried out or performed using random effects on comparable outcomes with the RevMan statistical software, a software built by Cochrane collaboration for meta-analysis [55,56]. In the present study, statistical tools and tests were deployed to analyze and test the generated data. Each of these tools and tests was chosen based on the research objectives and the nature of the data. Descriptive Statistics: Mean and proportion. These were used to summarize the central tendency of

continuous variables like hemoglobin levels and percentages. Descriptive statistics provided a clear overview of the data, helping to understand the typical values and variation in measurements before and after treatment [57]. Random effect meta-analysis was used to compare groups and subgroups, and for the determination of homogeneity of data obtained from the selected studies.

Ethical consideration: Following the fact that the review depended on already published data (secondary data) available in the public domain for public use, ethical clearance was not required for the commencement of the study. However, all used data from the secondary sources were duly cited.

Results

Figure-3 above shows the PRISMA flowchart illustrating the review process. Out of449 studies, 10 were considered eligible for quality assessment and onward data extraction.

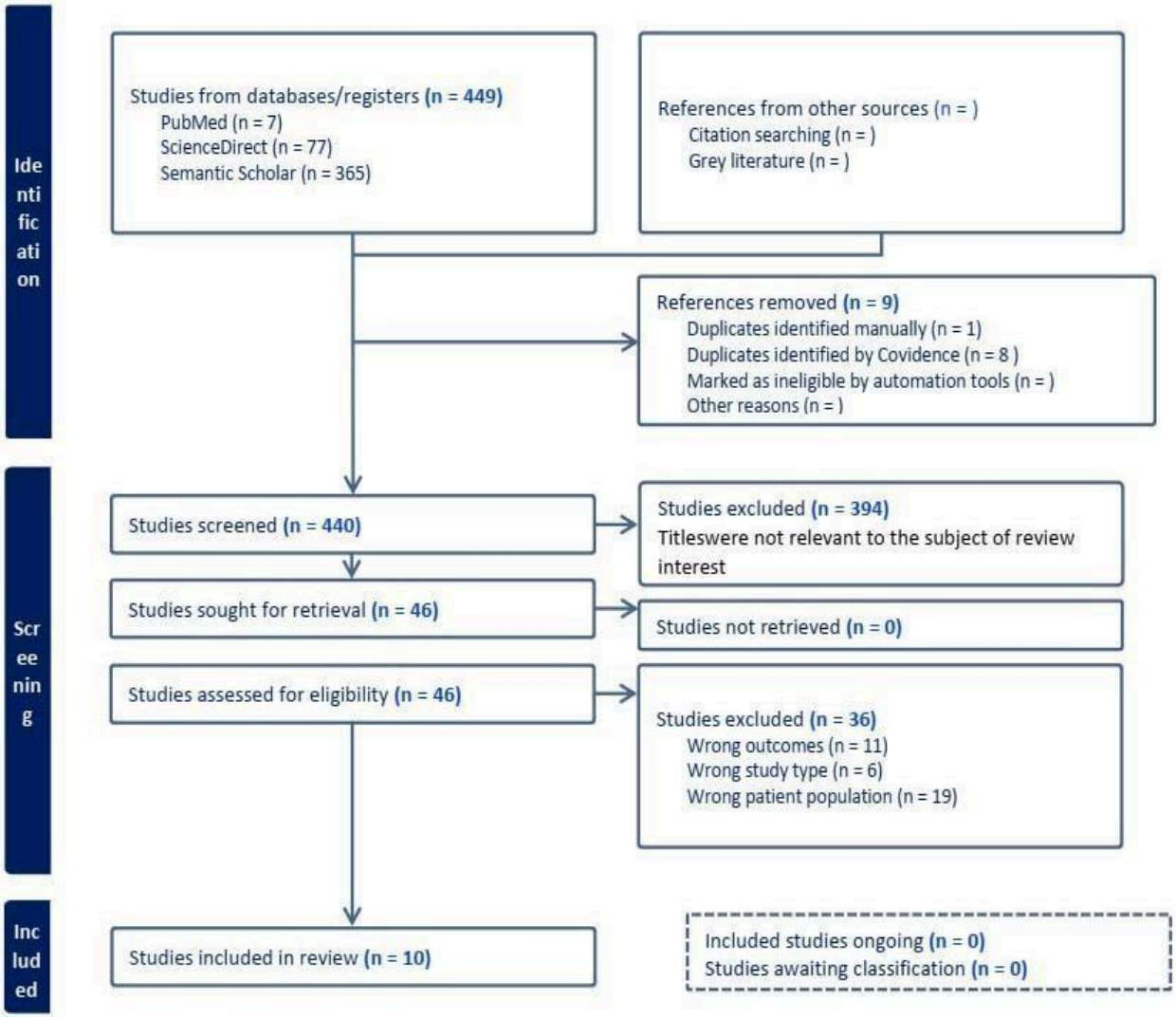

Figure-3: *PRISMA Flowchart*

Table-2: *Characteristics and result summaries of eligible studies*

Study	Study Design	Study Population	Treatment	PTAinterval	Summary of the findings
Studies on Lentivirus gene therapy					
Kanter et al., 2022 [58]	Non-randomized clinical trial	SCD patients; **Sample size**:35; **Mean age**: 24 yrs	LentiGlobin gene; **Dose(CD34+) (cells/Kg):** 6.9×10^6	17months	The study demonstrated significant hematologic improvement, with hemoglobin levels increasing from 8.5 to 11 g/dL following treatment. The therapy achieved 40% HbAT87Q expression, accompanied by substantial clinical benefits including reduction of vaso-occlusive pain to 12% and non-cardiac pain to 34%
Esrick et al., 2021 [59]	Phase 1/2 clinical trial	Severe SCD patients; **Sample size**: 6 **Mean age**: 14.3 yrs	BCL11A shmiR; **Dose(CD34+) (cells/Kg):** 6.6x10^6	18months	The study reported hemoglobin elevation from 9.3 to 11.4 g/dL alongside 28.5% HbF production. The study also documented notable decreases in hemolytic markers, with absolute reticulocyte count declining from 427,500 to 224,500 cells/mL and lactate dehydrogenase levels reducing from 446.5 to 303 U/L.
Magrin et al., 2019 [60]	Phase 1/2 clinical trial	SCD patients **Sample size**: 3 **Mean age**: 16.7 yrs	LentiGlobin gene; **Dose(CD34+) (cells/Kg):** 4.4x10^6	28.7 months	The study observed post-treatment hemoglobin levels of 10.7 g/dL with 22.7% HbAT87Q, though clinical outcomes showed persistent vaso-occlusive pain (66.7%) and chest pain syndrome (33.3%) in some patients.
Bonner et al., 2019 [61]	Phase 1/2 clinical trial	SCD patients **Sample size**: 13 **Mean age**: n/m	LentiGlobin gene; **Dose(CD34+) (cells/Kg):** n/m	n/m	The study achieved the highest HbAT87Q levels across studies at 85%, indicating strong therapeutic gene expression, though complete hematologic and clinical data were not available.
Malik et al., 2018 [62]	Phase 1/2 clinical trial	Severe SCD patients **Sample size**: 2 **Mean age**: 30yrs	Modified γ-Globin lentiviral vector; **Dose(CD34+) (cells/Kg):** 4.0x10^6	18months	The study demonstrated hemoglobin improvement from 8 to 10.6 g/dL with 20.5% HbF production, while noting that half of treated patients continued to experience non-cardiac pain.

Study	Study Design	Study Population	Treatment	PTAinterval	Summary of the findings
Tisdale et al., 2018 [63]	Phase 1/2 clinical trial	Severe SCD patients **Sample size**: 11 **Mean age**: 25 yrs	BB305 lentiviral vector; **Dose(CD34+) (cells/Kg):** 7.1x10^6	3months	The study reported hemoglobin levels reaching 10.5 g/dL with 39% HbAT87Q expression, though some patients still exhibited vaso-occlusive pain (33.3%) and non-cardiac pain (50%).
Hebert et al., 2018 [64]	Phase 1/2 clinical trial	SCD patients **Sample size**: 3 **Mean age**: n/m	LentiGlobin gene; **Dose(CD34+) (cells/Kg):** n/m	25months	The study documented post-treatment hemoglobin of 10.3 g/dL with 28.1% HbAT87Q, with chest pain syndrome persisting in 33.3% of cases but no treatment-related hospitalizations.
Studies on Hydroxyurea therapy					
Lad et al., 2022 [65]	Clinical trial	SCD patients **Sample size**: 138 **Mean age**: ≤14 yrs	Hydoxyurea; **Dose(CD34+) (cells/Kg):**18.7	24 months	The study showed that post-treatment hemoglobin levels averaged 9.2 g/dL with 25.6% HbF production. Clinical outcomes showed minimal vaso-occlusive pain (3.6%) and no chest pain, though non-cardiac pain remained prevalent at 54.3%. Hospitalization data was not reported
Hoppe et al., 1999 [66]	Clinical trial	Severe SCD patients **Sample size**: 8 **Mean age**: 3.7 yrs	Hydroxyurea; **Dose(CD34+) (cells/Kg):** 27	137 weeks	The study demonstrated the highest hemoglobin improvement among hydroxyurea studies (10.7 g/dL) with 19% HbF. Notably eliminated all vaso-occlusive and non-cardiac pain, but reported a 20% hospitalization rate post-treatment
Ofakunrin et al., 2018 [67]	Quasi-experimental study	SCA patients Sample size: 54 Mean age: 8.4 yrs	Hydroxyurea; **Dose(CD34+) (cells/Kg):** n/m	12 months	The study achieved hemoglobin levels of 9.3 g/dL, though HbF percentages were not documented. The study reported complete resolution of both vaso-occlusive and non-cardiac pain (0% for both), with no reported hospitalizations.

PTA interval: Post-treatment assessment interval; SCD: Sickle cell disease; SCA: Sickle cell anaemia; n/m: Not mentioned

Meta-analysis of the efficacy of a treatment (Lentivirus gene therapy) in managing sickle cell disease based on Haemoglobin

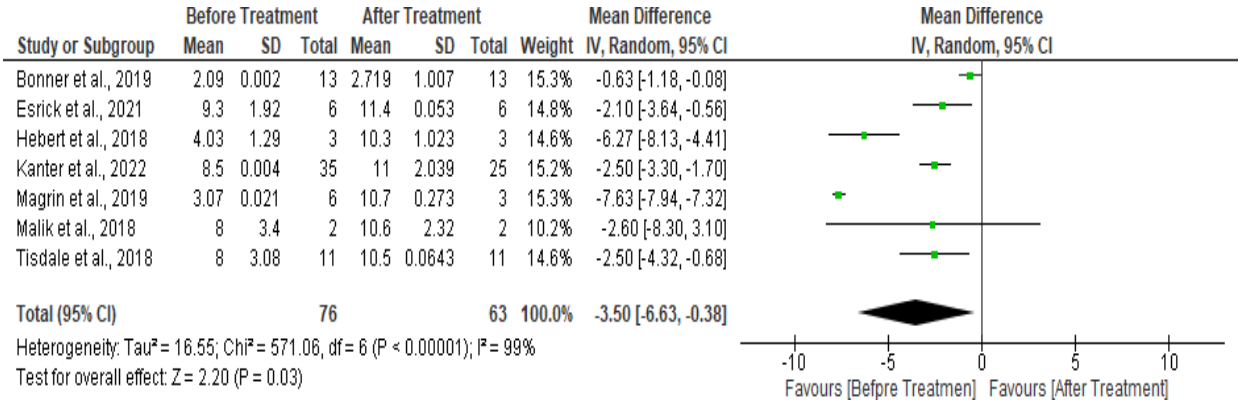

Figure-4: *Forest Plot illustrating meta-analysis of the efficacy of a treatment (Lentivirus gene therapy) in managing sickle cell disease based on Haemoglobin*

Figure-4 shows that among the seven studies, there was statistical difference among the groups of the studies (Z=2.20, P<0.03). This implies significant reduction in Hemoglobin before gene therapy (MD= -3.50, 95% C.I [-6.63,
-0.38]). Also, significant heterogeneity was seen across the studies (I2= 99%; P<0.00001).

Table-3 below shows the results of absolute reticulocyte count (ARC) and lactate dehydrogenase (LD) before and after the intervention. The result showed a decline in the ARC and LD levels after the lentivirus gene therapy.

Table-3: *Summary of the efficacy of a treatment (lentivirus gene therapy) in managing sickle cell disease*

Study	Absolute reticulocyte count (ARC) (cell/ml) before treatment	Absolute reticulocyte count (ARC) (cell/ml) after treatment	Lactate dehydrogenase (LD) (U/liter) before treatment	Lactate dehydrogenase (LD) (U/liter) after treatment
Kanter et al., 2022 [58]	280000	180000	400	250
Esrick et al., 2021 [59]	427500	224500	446.5	303
Magrin et al., 2019 [60]	-	-	-	-
Bonner et al., 2019 [61]	-	-	-	-
Malik et al., 2018 [62]	-	-	-	-
Tisdale et al., 2018 [63]	-	-	-	-
Hebert et al., 2018 [64]	-	-	-	-

The results from Table-4 below show Kanter et al. reported a treatment percentage of 40% for HbAT87Q, while Esrick et al. reported a percentage of 28.5% for HbF [58,59]. These values represent the proportions of these components in their respective treatments. Similarly, Magrin et al. reported a treatment percentage of 22.7% for HbAT87Q, and Bonner et al. reported a high percentage of 85% for HbAT87Q [60,61]. Malik et al. reported a treatment percentage of 20.5% for HbF [62], while Tisdale et al. and Hebert et al. reported a percentage of 39% and 28.1% for HbAT87Q respectively [63,64].

Table-4: *Proportion of HBAT87Q and HbF among the studies*

Study	Percentage of HbAT87Q (%) treatment	Percentage of HbF (%)
Kanter et al., 2022 [58]	40	-
Esrick et al., 2021 [59]	-	28.5
Magrin et al., 2019 [60]	22.7	-
Bonner et al., 2019 [61]	85	-
Malik et al., 2018 [62]	-	20.5
Tisdale et al., 2018 [63]	39	-
Hebert et al., 2018 [64]	28.1	-

Table-5 summarizes the results of the proportions of clinical outcomes related to vaso-occlusive pain, chest pain syndrome, hospitalization, and non-cardiac pain in various studies. Kanter et al. (2022) reported vaso-occlusive pain percentage of 12% and non-cardiac pain of 34% [58]. They did not provide data for chest pain syndrome or hospitalization. Magrin et al. reported a high vaso-occlusive pain percentage of 66.7% and chest pain syndrome of 33.3% [60]. They did not provide data for hospitalization or non-cardiac pain. Malik et al. reported that 50% of patients had non-cardiac without providing information on vaso-occlusive pain, chest pain syndrome, or hospital stays [62]. Tisdale et al. found that 33.3% had vaso-occlusive pain and 50% had non-cardiac pain, while the research did not report on chest pain syndrome or hospitalizations [63]. Hebert et al. reported chest pain syndrome in 33.3% of patients but did not provide any information concerning vaso-occlusive pain, non-cardiac pain, or hospital stays [64]. Esrick et al. and Bonner et al. did not give any data on these clinical outcomes [59,61].

Table-5: *Proportion of the clinical outcomes*

Study	Vaso-occlusive pain (%)	Chest pain syndrome (%)	Hospitalization (%)	Non-cardiac pain (%)
Kanter et al., 2022 [58]	12	-	-	34
Esrick et al., 2021 [59]	-	-	-	-
Magrin et al., 2019 [60]	66.7	33.3	-	-
Bonner et al., 2019 [61]	-	-	-	-
Malik et al., 2018 [62]	-	-	-	50
Tisdale et al., 2018 [63]	33.3	-	-	50
Hebert et al., 2018 [64]	-	33.3	-	-

Age dependent variation in treatment outcome

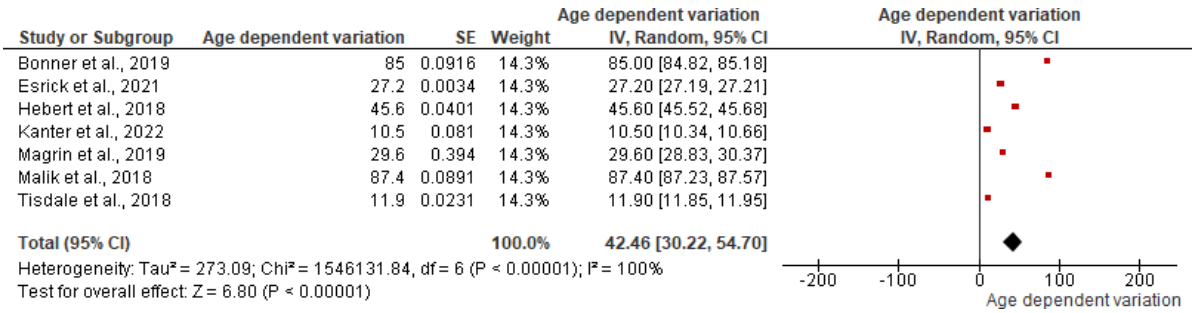

Figure-5: *Forest Plot for Pooled effect of age dependent variation in treatment outcomes across the studies*

The forest plot in Figure-5 above demonstrated the age dependent variation in treatment outcomes across the studies. There was a significant difference across the studies based on age dependent variation in treatment outcome (Z^2=6.80 [P<0.00001]). The pooled effect revealed significant age variation across the study participants (IV=42.46, 95% C.I [30.22, 54.70]).

Significant heterogeneity among the studies was also detected (I^2=100%).

Table-6 provides a summary of descriptive statistics related to age-dependent variation in treatment outcomes for sickle cell disease across different studies. The table includes data on the ages of individuals who participated in the studies. The average age of the participants across all studies is approximately 22 years, with an age interval spanning from 14 to 32 years. The table presents various treatment outcomes, including the percentage of HbAT87Q treatment, the percentage of HbF treatment, absolute reticulocyte count (ARC) after treatment, and lactate dehydrogenase (LD) levels after treatment.

Table-6: *Summary of descriptive statistics on age dependent variation in treatment outcome*

Study	Age	Percentage of HbAT87Q (%) treatment	Percentage of HbF (%)	Absolute reticulocyte count (ARC) (cell/ml) after treatment	Lactate dehydrogenase (U/liter) after treatment
Kanter et al., 2022 [58]	24	40	-	180000	250
Esrick et al., 2021 [59]	14.3	-	28.5	224500	303
Magrin et al., 2019 [60]	16.7	22.7	-	-	-
Bonner et al., 2019 [61]	-	85	-	-	-
Malik et al., 2018 [62]	30	-	20.5	-	-
Tisdale et al., 2018 [63]	25	39	-	-	-
Hebert et al., 2018 [64]	-	28.1	-	-	-
Average Age	**22**				
Age Interval	**14–32**				

Meta-analysis of treatment outcome based on mode of action of lentiviral gene therapy

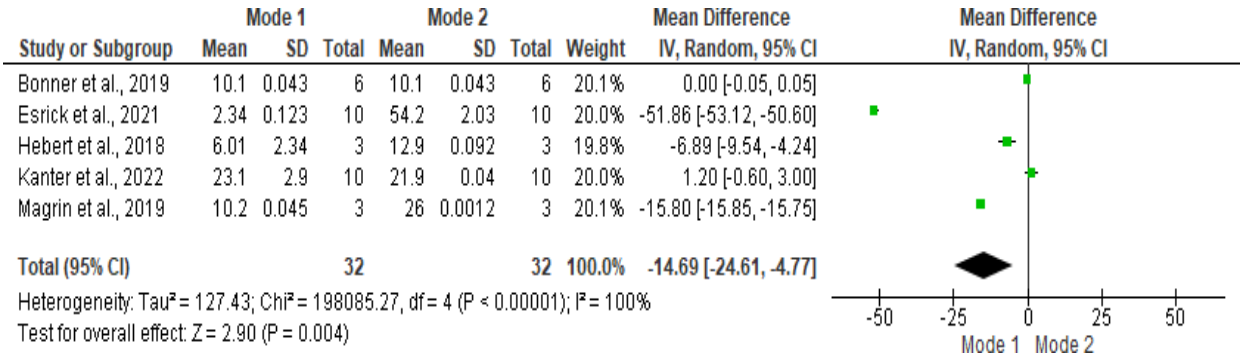

Figure-6: *Forest plot showing the treatment outcome based on Mode of action of lentiviral gene therapy.*
Mode 1: represents treatment targeted at improving the corrected mutant gene (HbAT87Q)
Mode 2: represents treatment targeted at improving HbF level.

Figure-6 below shows the meta-analysis of treatment outcome based on mode of action of lentiviral gene therapy across the studies. It was seen that there was a significant mean difference between the mode 1 and mode 2 groups and

Lentiviral gene therapy favoured mode 1 action (IV=-14.69, 95% CI [-24.61, -4.77], Z=2.90, p=0.004).
Significant heterogeneity existed among the groups (I^2= 100%, P<0.00001).

Treatment outcome based on disease severity

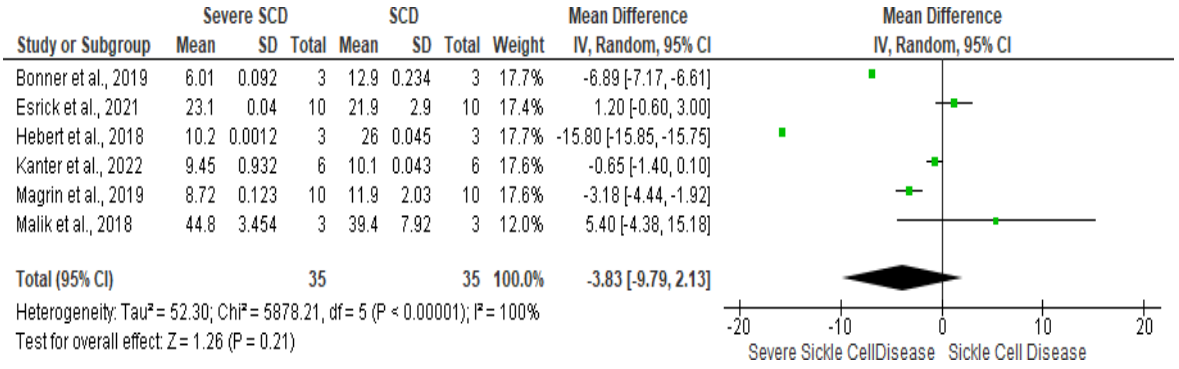

Figure-7: *Forest Plot showing treatment outcome based on disease severity (SSCD versus SCD)*

Further Meta-analysis was conducted to treatment outcome based on disease severity (SSCD versus SCD) among the studies (Figure-7). There was no significant difference in the treatment effect in

both groups (IV=-3.83, 95% [-9.79, 2.13], Z=-1.26). There was significant heterogeneity among the studies (I^2=100%).

Meta-analysis of treatment outcome based on duration of treatment assessment

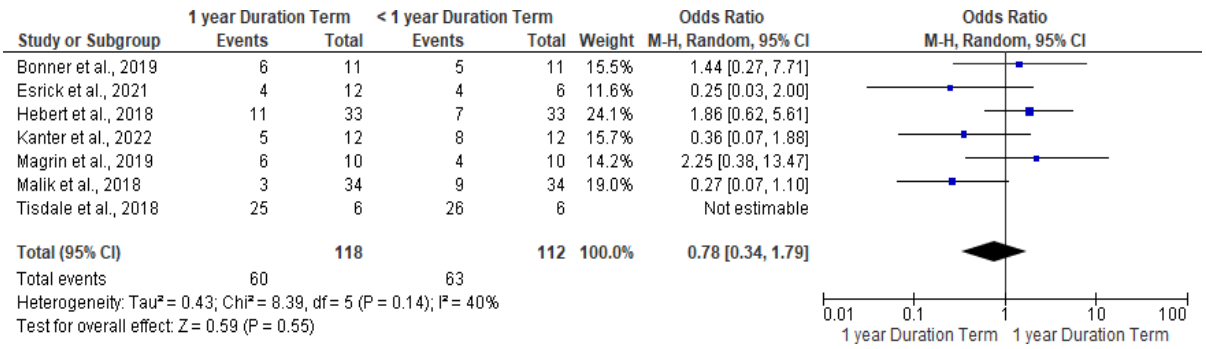

Figure-8: *Forest plot showing treatment outcome based on duration*

Based on Figure-8 as illustrated, the meta-analysis of treatment outcome based on duration of treatment assessment revealed no effect for

duration of treatment assessment at 1 year duration term and <1 year duration term (OR, 0.78, 95% [0.34, 1.79), Z=0.59, p=0.55).

Meta-analysis of treatment outcome between lentivirus gene therapy and hydroxyurea for SCD

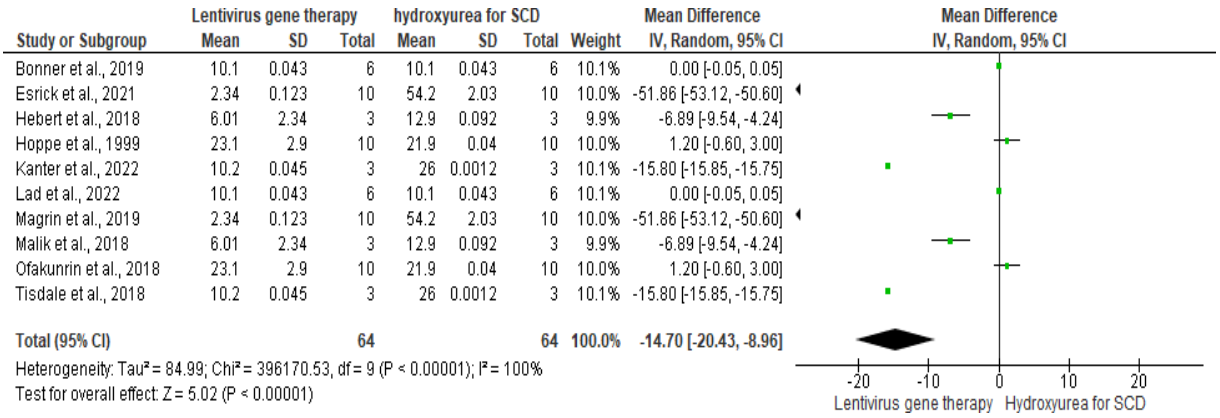

Figure-9: *Forest Plot Showing meta-analysis of treatment outcome between lentivirus gene therapy and hydroxyurea for SCD*

The meta analysis of treatment outcome between lentivirus gene therapy and hydroxyurea for SCD were estimated in Figure-9 below. It was revealed that lentivirus gene therapy improved treatment outcomes compared to hydroxyurea for SCD (IV, -14.70, 95%, [-20.43, -8.96] Z=5.02, P<0.00001). Significant heterogeneity was observed in the studies (I^2=100%).

Table-7 presents a summary of descriptive statistics comparing treatment outcome (HbF) between two different approaches for managing sickle cell disease (SCD): lentivirus gene therapy and hydroxyurea treatment.

In lentivirus gene therapy, the percentage of HbF (%), an important indicator in SCD treatment, also varies among the studies. Esrick et al. (2021) reported a percentage of HbF of 28.5%, indicating the presence of a significant amount of fetal hemoglobin after lentivirus gene therapy [59]. Malik et al. reported a percentage of HbF of 20.5% [62]. Some studies did not provide data for certain treatment outcomes. In hydroxyurea treatment, the percentage of HbF (%), similarly, varies between studies. Lad et al., 2022, reported a percentage of HbF of 25.6%, while Hoppe et al. reported a percentage of HbF of 19% [65,66]. Like the lentivirus gene therapy section, some studies did not provide data for certain treatment outcomes.

Table-7: *Summary of descriptive statistics on treatment outcome between lentivirus gene therapy and hydroxyurea for SCD based on HbF level*

Study	Percentage of HbF (%)
Lentivirus gene therapy	
Kanter et al., 2022 [58]	-
Esrick et al., 2021 [59]	28.5
Magrin et al., 2019 [60]	-
Bonner et al., 2019 [61]	-
Malik et al., 2018 [62]	20.5
Tisdale et al., 2018 [63]	-
Hebert et al., 2018 [64]	-
Hydroxyurea treatment	
Lad et al., 2022 [65]	25.6
Hoppe et al., 1999 [66]	19
Ofakunrin et al., 2018 [67]	-

Comparison clinical outcome between lentivirus gene therapy and Hydroxyurea for SCD

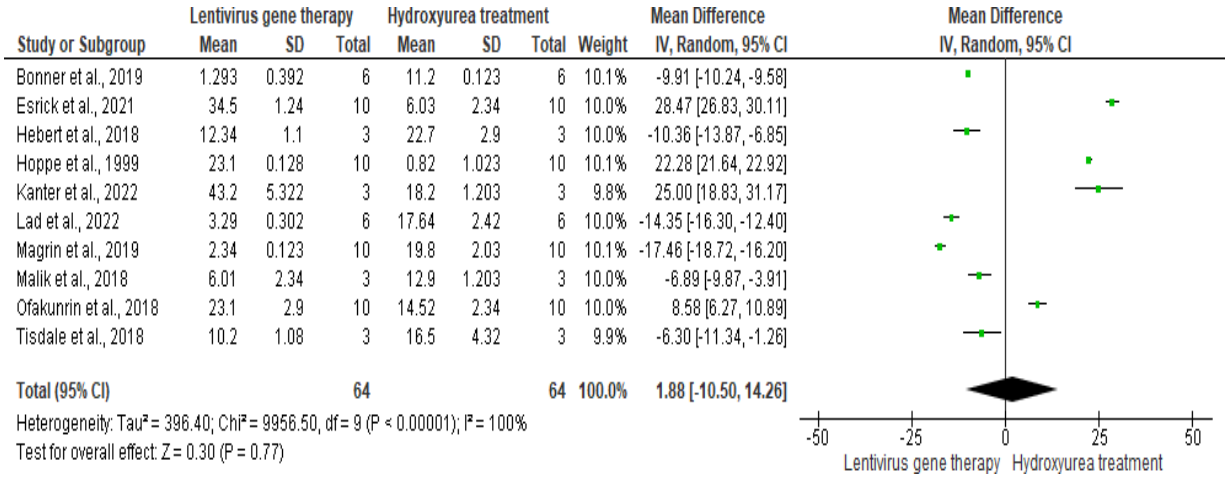

Figure-10: *Forest plot showing the comparison of clinical outcomes between lentivirus gene therapy and Hydroxyurea for SCD*

The meta-analysis of the comparison of clinical outcomes between lentivirus gene therapy and hydroxyurea for SCD (Figure-10) showed that there was no significant difference between lentivirus gene therapy and hydroxyurea for SCD (IV=1.88, 95%, [-10.50, 14.26], Z=0.30, P=0.77). There wassignificant heterogeneity among the studies (I^2=100%, P<0.00001).

Discussion

Studies suggest, LGT (gene therapy) consistently raised hemoglobin levels (10.3–11.4 g/dL) and lowered markers of red blood cell breakdown. Treatments using the HbAT87Q approach (up to 85% effectiveness) worked better than those focused on increasing HbF (up to 28.5%) [58–64]. Clinical outcomes varied, with some patients experiencing residual pain despite hematologic improvement. When compared to hydroxyurea, LGT achieved higher hemoglobin levels (9.2–10.7 g/dL with hydroxyurea) without hospitalizations, though both therapies showed comparable reductions in clinical complications [65,66]. The durability of treatment benefits was evident in studies with follow-up periods exceeding one year, supporting LGT as a transformative, but not yet perfect, therapy for sickle cell disease.

The substantial increase in Hb levels indicated a positive response to the therapy, as higher Hb levels are generally desirable in managing sickle cell disease. A reduction in absolute reticulocyte count (ARC) is typically seen as a positive response to treatment in sickle cell disease as well as a decrease in lactate dehydrogenase (LD) levels. All these changes in the parameters are often indicative of improved red blood cell health. These findings are in consonance with the study conducted by Abraham in 2021 who reported that increase in Hb level is an indication of improvement of red blood cell health and treatment success [25,68]. This is to say that the decrease in ARC and LD levels reported in this review were suggestive of therapeutic success of LGT in SCD patients whose red blood cells were often destroyed or lysed due to their sickle shape. In general, the increase in Hb, and decrease in ARC and LD levels suggested that the therapy was effective in improving the health of individuals with SCD [69].

Considering HbAT87Q and HbF levels in the studies reviewed, it is evident that HbAT87Q level rose as high as 85% while HbF levels rose as high as 28.5% of the total haemoglobin. This suggests that LGT using HbAT87Q correction might lead to better results for raising hemoglobin levels than

approaches focusing on HbF. However, care should be taken about drawing conclusions because only two studies looked at HbF, which may not be sufficient to make the comparison reliable. It is important to mention that LGT reviewed in this study had two kinds of intervention; the lentivirus gene intended to correct the mutant gene thus promoting HbAT87Q [70], and the LGT intended to increase HbF level [33]. Higher HbF is intended to decrease HbS polymerization, and thus less likely to promote sickle cell formation that is associated with vaso-occlusion, anaemia and organ damage [71]. Again, since the HbF intervention outcome is not intended to correct the mutant gene but rather suppress its polymerization, the low percentage contribution HbF level to the total Hb level is logically supported.

Clinical outcomes such as vaso-occlusive pain, chest pain syndrome, hospitalization and non-cardiac pain were assessed among the studies. The findings revealed that there were no reported cases of hospitalization after treatment although there were few reported cases of vaso-occlusive pain [58,60,63], chest pain syndrome [60,64], and non-cardiac pain [58,60,63]. These findings support the fact that LGT improves the quality of life as reported by other studies [58,72-74].

The data in Table-6 showed that individuals of different ages participated in these studies, ranging from young adolescents to adults. This age variation allowed for an exploration of how age may influence treatment outcomes. For example, Kanter et al. reported that individuals with an average age of 24 years showed improvements in Hb levels and about 40% of them responded well to HbAT87Q treatment. Esrick et al. observed positive treatment outcomes in individuals with an average age of 14.3 years, including higher Hb levels and a percentage of HbF treatment of 28.5% [59]. Magrin et al. included individuals with an average age of
16.7 years, showing improvements in Hb levels and a percentage of HbAT87Q treatment of 22.7% [60]. Although all age levels, ranging from 14-32 years, had improvements in the measured outcomes, the effect of the treatment varied significantly depending on the age of the subjects. This report is consistent with the view of other researchers who reported a possibility of age dependence outcome in gene treatment interventions [75,70].

It is noteworthy that LGT provides therapeutic intervention via any of the two mechanisms: gene addition [16] and promoting HbF production [25-33]. In comparing between modes of treatment, since the results showed that there was significant improvement in the treatment outcome in mode 1 compared to mode 1I, it implies that the LGT was more effective when the treatment was targeted towards correcting the mutant gene than when treatment was targeted towards improving HbF level. This means that whether the LGT was made to fix the faulty gene or to increase fetal hemoglobin levels, both approaches showed better treatment result, although correcting the mutant gene provided better therapeutic achievement than improving foetal haemoglobin level.Till now, no study has compared the treatment outcomes between these two modes. The study conducted by Demirci and Germino-Watnick who reported improvements in total Hb levels in lentiGlobin gene and BCL11A shmiR gene infusion [33,76] supports the fact that both modes of treatments achieved therapeutic success.

The findings obtained in comparing LGT outcomes between severities of SCD showed no significant difference. This implies that the severity of the disease does not play any role in treatment outcome of LGT. Although earlier findings from this study have reported treatment improvement in all SCD patients, the severity status of SCD did not impact differential treatment benefit on the efficacy of LGT when patients with SCD and severe SCD treatment outcomes were compared. This implies that the LGT achievement does not segregate between patient with mild SCD and those with severe SCD. This may be supported with the clinical outcomes result that showed that there was a decline in the SCD crisis after LGT treatment in all studies irrespective of the SCD severity [58,60,63].

The result presented in Figure-6 highlighted the diversity in the duration of treatment assessment across the studies, however, the duration of the treatment (whether long term or short term) did not make any difference in the success achieved. This may be due to the sustained presence of the corrected gene in the haematopoietic stem cell infused in the treatment process, resulting in continuous production of healthy red blood cells

and improved treatment outcome. This is supported by the works conducted by Kanter and Drakopoulou in 2021 and 2022 respectively who reported long term effectiveness of LGT [16,78].

In comparing LGT and HU treatment in terms of Hb levels after treatment, both approaches showed significant variability among studies, with patients treated with LGT having better treatment outcome compared to those on HU treatment. This suggests that while HU has long been used to help people with SCD and is supported by the American Society of Hematology, the new treatment LGT seems to work even better. LGT gives new hope for improving how SCD is treated and managed. Also, LGT is given just once, while HU needs to be taken regularly, making LGT even more beneficial compared to HU [78,79].

When it comes to the percentage of HbF, it appears that lentivirus gene therapy, as seen in Esrick et al. [59], and Malik et al. [62] resulted in slightly higher percentages compared to HU treatment. However, it is important to note that these changes may be due to chance, or on various factors, including individual patient characteristics, the specific protocol used in each study, mechanism of drug action and the duration of treatment.

Generally, there was no significant difference in the clinical outcomes (vaso-occlusive pain, chest pain syndrome and non-cardiac pain) between LGT and HU treatment among SCD patients. However, those who were treated with LGT had no case of hospitalization after the treatment but in HU treated, a report by Hoppe and his colleagues in 1999 reported that 20% of the SCD patients were re-hospitalized after HU treatment [66]. This implies that both treatments were able to provide similar treatment effectiveness to the patients.

Some safety concerns were identified in course of this review. One study identified some safety concerns such as occurrence of Type 1 diabetes and respiratory infection, but he reported those adverse effects were not necessarily related to the effect of the administered treatment (LGT) [59]. Hydroxyurea treatment was reported to have a few safety concerns also such as leucopenia, myelosuppression, brain infarction. However, although there was no leading or most frequent safety issue identified, leucopenia was consistent in both HU treatment and LGT. This may be due to the impact the treatments have on haematopoietic system and bone marrow. Studies have established a dose-dependent relationship of leucopenia occurrence in HU [80]. Based on previous reports by Kanter and Ofakunrin, the leucopenia may be due to neutropenia which gave rise to the condition febrile neutropenia reported by them [16,61]. Contrarily, Lad and his colleagues did not identify any adverse effect after the administration of HU [67].

Although LGT for sickle cell disease shows promising outcomes in the initial trials, there are however certain criticisms that must be addressed to advance its clinical application. While LGT demonstrates promising efficacy in increasing hemoglobin levels and reducing clinical complications, the current evidence is limited by the predominance of early-phase trials with small sample sizes and short follow-up periods, leaving long-term safety and durability of therapeutic effects unresolved. Notably, the mechanisms underlying age-dependent treatment responses remain unclear, particularly whether pediatric patients, with their more active haematopoietic systems, derive greater benefits than adults. Additionally, while LGT targeting HbAT87Q correction appears superior to HbF induction, the biological rationale for this difference warrants deeper investigation, including potential synergies between the two approaches. Disease severity did not significantly influence outcomes, but patient heterogeneity, including genetic variations in SCD subtypes, was not thoroughly examined, suggesting a need for stratified analyses. There are not enough studies comparing LGT with other new treatments like CRISPR gene editing or stem cell transplants, so it is still not known which is safer, more effective, or more affordable. The safety data available is incomplete, especially concerning side effects such as neutropenia and gastroenteritis, which necessitate further reporting and research. Besides medical results, there are also real-world challenges like high costs, limited production capacity, and ethical concerns that need to be solved to make LGT available to everyone. Future research should focus on long-term studies, direct comparisons with other treatments, and finding markers to track how well it works. Filling these

gaps could help turn LGT into a widely available and life-changing cure for SCD, customized for different patients and types of the disease.

Conclusion

This study comprehensively examined the efficacy, clinical outcomes, and safety of LGT for sickle cell disease (SCD) in comparison with HU. This review has revealed that although both treatment interventions provided improvement in the laboratory data like haemoglobin level, LGT had better treatment achievement compared to HU. While both treatments had improvements in the clinical outcomes, there was no significant difference in the improvement levels between both treatments. This suggests that both treatment approaches have comparable outcomes in terms of managing these clinical manifestations of SCD.

Considering factors that may affect the efficacy of LGT, age, mode of treatment, severity of the disease and duration of treatment follow-up were studied, and this review reported that age of the patient may have an effect on the efficacy of the treatment. Similarly, the LGT mechanism that favours addition of the corrected sickle cell gene provides better treatment efficacy than LGT mechanism that enhances HbF production. Also, the treatment remained effective after one year. People who were checked before one year and those checked after one year showed similar improvements. Both interventions, however, reported safety concerns. Certain adverse effects like neutropenia and gastroenteritis were reported in both LGT and HU treatment of SCD which requires further investigations and research to improve patient safety.

Recommendations

To gain better comprehensive understanding of the comparative effectiveness of these treatments and their long-term impact on the quality of life for individuals with SCD, further research, including large-scale clinical trials and extended follow-up studies is imperative. Since LGT has better efficacy and comparable safety concerns with HU, LGT may be considered a better treatment option for SCD patients. Owing to the fact there were limited studies in LGT, most studies on LGT were currently non-randomized clinical trials, and therefore, it is recommended that future studies should be designed as randomized controlled clinical trials. Further research should build upon the lessons learned from early clinical trials and preclinical models to refine treatment protocols and enhance the safety profile of LGT.

Limitation

Since LGT is an emerging therapy gaining research interest in clinical trials, there were limited primary studies on this therapy and as such may affect the quality of the evidence or conclusion generated from this review. Also, the few available studies were in their phase 1/2 of clinical trial and as such, the sample size in each study was not adequate enough to make strong inferences on the population because they do not meet the statistical requirement for adequate population representativeness.

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Author's contributions

SD developed the manuscript. CFA performed the meta-analysis and other statistics. IMK and PUE Reviewed and edited the work.

Conflict of interest

Authors declared no conflict of interest

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