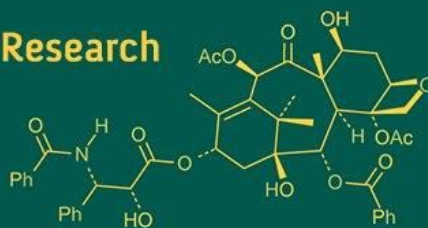


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Pragati Gupta
 Department of Zoology, Guru
 Ghasidas Vishwavidyalaya,
 Bilaspur, Chhattisgarh, India

Meenoo Kumbhkar
 Department of Zoology, Guru
 Ghasidas Vishwavidyalaya,
 Bilaspur, Chhattisgarh, India

Shani Raj
 Department of Horticulture,
 BTC College of Agriculture and
 Research Station, IGKV,
 Bilaspur, Chhattisgarh, India

Advances in therapeutic approaches: Hydroxyurea, stem cell transplantation, and gene therapy

Pragati Gupta, Meenoo Kumbhkar and Shani Raj

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Abstract

The mortality and morbidity rates associated with sickle cell disease (SCD) are significant all over the globe; however, they are particularly high in regions where the illness is prevalent, such as India, the Middle East, and sub-Saharan Africa. Over the course of the last three decades, advancements in therapeutic intervention have brought about a revolution in the treatment of sickness. This change in emphasis from symptomatic therapy to curative and customized treatments has occurred. The Food and Drug Administration (FDA) first authorized hydroxyurea as a medication to treat sickle cell disease (SCD). Acute chest syndrome, vaso-occlusive crises, and transfusion requirements are all alleviated. However, there are a number of drawbacks to this therapy, including issues with accessibility, long-term safety, and the variability in patient response. Stem cell transplantation, and in particular allogeneic hematopoietic stem cell transplantation (HSCT), presents a promising therapeutic alternative; yet, its use is limited by a multitude of circumstances. Donor availability, risk of graft-versus-host disease, and financial constraints are all relevant considerations. The use of viral vector systems, CRISPR-Cas9, and molecular genetics, among other recent developments in gene therapy, have shown promising clinical research prospects as a method to correct or compensate for the underlying mutation in the β -globin gene. The results of meta-analyses, PRISMA-based systematic reviews, and visual comparisons are all a part of this study. A combination of recent findings in genetics, treatment effectiveness, and epidemiological data forms the basis of the research. We can show how treatments work, how genes work, and what the future holds by using visualization tools like histograms, forest plots, and route diagrams. Our main goal is to promote sickle cell disease (SCD) precision medicine by connecting molecular genetics with clinical applications. In the article's latter sections, the essayists highlight the need of ensuring that diverse populations have fair access to novel treatments, as well as the current constraints and financial obstacles.

Keywords: Hydroxyurea, stem cell transplantation, gene therapy, sickle cell disease, genetics, epidemiology, and therapeutics

Introduction

Instead of the typically occurring glutamic acid at position six in the beta-globin protein, a single point mutation in the gene codes for valine ^[1]. Because of this, hemoglobin S (HbS) is formed. The occurrence of SCD is caused by this particular mutation. Porosity causes hemoglobin S to polymerize, which in turn causes red blood cells to take on a sickle shape ^[2]. This kind of red blood cell cannot transport oxygen due to its makeup, which includes hemoglobin S. Red blood cell abnormalities and elevated adhesion molecule surface expression have the potential to cause vascular occlusion, a life-threatening vaso-occlusive crisis (VOC), and tissue and organ damage in the long run ^[3]. Among hereditary monogenic disorders, sickle cell disease (SCD) ranks high.

This problem disproportionately affects African-Americans. On a yearly basis, 3,000 American infants are diagnosed with sickle cell disease (SCD), which affects an estimated 80,000 to 100,000 Americans ^[4]. Approximately 20 million individuals throughout the globe are coping with sickle cell disease. The fraction of pediatric patients who made it through the ordeal was higher due to early intervention, preventive measures, and neonatal screening programs. Sickle cell disease (SCD) patients, on the other hand, are believed to have a life expectancy around twenty years lower than the general population. The National Institutes of Health Cure Sickle Cell program is a patient-centered research initiative that aims to discover viable genetic therapeutics for sickle cell disease.

Corresponding Author:
Pragati Gupta
 Department of Zoology, Guru
 Ghasidas Vishwavidyalaya,
 Bilaspur, Chhattisgarh, India

The study of sickle cell disease is the principal goal of the endeavor. It requires teamwork. By increasing awareness of fundamental research, clinical trials, and patient support, educational and community engagement initiatives promise to benefit greatly from this concerted effort to aid in the development of therapeutic therapies [5].

This effort has the potential to greatly benefit all of these pursuits. Pain and symptom relief are the primary goals of conventional sickle cell disease (SCD) treatments. Injecting erythrocytes, which are mostly constituted of hemoglobin A, is one of the reasons why medical experts may advise blood transfusions as a treatment for anemia or a means of preventing strokes [6]. Modern technology has made it feasible to do red blood cell exchanges, basic transfusions, and chronic transfusions. Blood transfusions include the risk of iron buildup, alloimmunization, and inadequate phenotypic matching, among other complications. The major goal of the first disease-modifying medication treatment, hydroxyurea, was to lessen the severity of the difficulties.

Life for sickle cell disease (SCD) patients has been greatly improved by the FDA-approved pain relievers L-glutamine, voxelotor, and crizanlizumab-tmca, as well as by other VOC reducers [7]. At this time, the only treatment option for sickle cell disease (SCD) is stem cell transplantation, which is also called hematopoietic stem cell transplantation (HSC). The recipient will obtain healthy erythrocytes when they receive allogeneic stem cells from a donor who does not possess the mutation [8]. This occurs as a result of the mutation's impact on the cells.

Although there are many benefits to allogeneic transplants, there is also a high risk of rejection and graft-versus-host disease (GVHD), which may be fatal or cause severe illness. To get around the most difficult part of finding an HLA-matched donor, haploidentical donors and cord blood might be used. An innovative method of treating sickle cell disease (SCD) that makes use of gene therapy to correct the genetic mutation that is the root cause of the disease is on the horizon. Because of this, it is possible that the sickness may be cured. It is possible to change the patient's native gene via gene therapy, or it may include introducing a new gene into the patient's body for the purpose of integration and expression. Gene therapy offers a variety of methods. In every one of these methods, one of the most important steps is the collection of the patient's HSCs, which are the treatment targets. After chemotherapy, the next step is to change the genetic code in a controlled environment before sending the cells back to the patient in order to remove any bone marrow that may still be present [9]. This concise summary of the treatment options for sickle cell disease (SCD) includes gene therapy as well as other current treatments.

Hydroxyurea

Patients with sickle cell disease who were 18 years old or older and had three or more severe crises in the previous year were eligible to receive hydroxyurea (HU) in 1998 as a disease-modifying drug (DMD) treatment, according to the United States Food and Drug Administration [10]. In order to prevent red blood cells (RBCs) from sickling and produce volatile organic compounds (VOCs), HU increases the quantity of fetal hemoglobin (HbF) and decreases the polymerization ability of hemoglobin S [11]. Moreover, HU may lower inflammatory mediator and circulating leukocyte

levels, which is a great advantage. At least 18-year-old boys and girls from 21 different clinics participated in an evaluation of sickle cell anemia.

The study was conducted in a randomized fashion with participants blinded. In order to be eligible to participate, individuals must have experienced three distinct kinds of crises during the last year. The yearly crisis rates were significantly different between the two groups: one treated with HU and another given a placebo. The difference was statistically significant (median, 2.5 crises per year versus 4.5 crises per year, $p < 0.001$). The findings from the study on human uterine stimulation demonstrated significantly longer median durations until first crisis (3.0 months compared to 1.5 months, $P = 0.01$) and second crisis (8.8 months compared to 4.6 months, $p < 0.001$).

The risk of chest symptoms (25 vs 51, $p < 0.001$) and the need for transfusions (48 vs 73, $P = 0.001$) was reduced in those who got HU treatment compared to all other patients. It is crucial to closely monitor its use, even if no serious side effects were observed. Benefits of HU did not become obvious right away, and it is likely that even at the highest possible dosages, there will be no therapeutic benefit [12]. In 2017, we were able to transfuse blood and alleviate painful crises for pediatric kids (those older than two) diagnosed with sickle cell disease (SCD) who experience recurrent moderate to severe crises, all with the blessing of the Humanitarian Union (HU).

Allogeneic hematopoietic stem cell transplantation

It requires a great deal of expertise for healthcare providers to give peri-transplant care to individuals with sickle cell disease. Compared to adults, the outcomes for patients under the age of 18 are often better. Patients with sickle cell disease in adults may need more time to recuperate from transplant-related organ damage caused by prolonged inflammation and toxicity. Because the harm to their organs has persisted for a longer duration, this is the case. Not much has changed about the seriousness of issues like delayed immune reconstitution and the aftereffects of infectious diseases. Furthermore, immunological responses may put those with sickle cell disease at risk of rejection. As the patient recovers, it will likely be required to undergo comprehensive red blood cell antigen matching before blood transfusions may be safely administered. Pharmacologically targeting the bone marrow microenvironment or modulating the function of mesenchymal stromal cells may be an option to improve the chimerism engraftment over a longer duration [13]. In theory, both of these options could work.

Gene therapy

The autologous HSCT offers a number of benefits over the allogeneic HSCT, including a decreased risk of major complications, an increased availability of donors, a lack of graft rejection and graft-versus-host disease (GVHD), and a more fast immune reconstitution. All of these advantages are in contrast to the allogeneic stem cell transplantation. It is not recommended that granulocyte colony-stimulating factor be used in the treatment of sickle cell disease (SCD) because to the significant adverse effects that it generates, despite the fact that it is useful as a mobilizing agent. Plerixafor, which is a CXCR4 antagonist, has shown encouraging outcomes in gene therapy studies for sickle cell disease [14, 15]. Patients who have sickle cell disease may be needed to undergo many cycles of mobilization and

apheresis collection. This is due to the fact that the level of mobilization that they have accomplished may not be sufficient. By including red blood cell exchange transfusions into a pretransplant preparation regimen, it is feasible to reduce the chance of complications associated with sickle cell disease (SCD) arising during the process of HSC mobilization and procurement. This includes reducing the likelihood of complications occurring throughout the procedure. For the purpose of preventing the effects of HbS and facilitating the maintenance of hematopoietic engraftment, it is necessary to modify the genes of autologous stem cells. possible approaches to gene therapy include the alteration of the HbA gene, the induction of hemoglobin F, and the correction of the HbS gene. All of these approaches are regarded to be possible strategies. There is a possibility that the lentiviral vector and conditioning treatment will result in insertional mutagenesis, which might then lead to subsequent cancers. It is possible that this will be one of the adverse effects that the therapy will have.

Objectives

1. To evaluate the therapeutic efficacy and limitations of hydroxyurea, gene therapy, and stem cell transplantation in the management of sickle cell disease.
2. To evaluate the potential benefits of various therapy methods in enhancing patient survival and quality of life, both now and in the future.

Research Methodology

This study is comprised of a meta-analysis and a systematic review, and it is conducted in accordance with the standards that are outlined in PRISMA 2020.

Eligibility Criteria

- **Population:** People who suffer from sickle cell disease or other ailments involving hemoglobin A.
- **Interventions:** Hydroxyurea, HSCT, and gene therapy/editing are all methods that include hematopoietic stem cells.
- **Comparators:** Treatment options include a placebo, the current medical standard or even alternative methods.
- **Outcomes:** Vaso-occlusive crises, hemoglobin/hemoglobin F levels, overall survival, survival without events, engraftment, independence from transfusions, adverse events.
- **Study Types:** As a means of establishing the context, high-quality reviews, clinical trials, cohort studies, and randomized controlled trials are described.

Search Strategy

A number of search keywords were used to search the following electronic databases: PubMed, Embase, Cochrane CENTRAL, Web of Science, and ClinicalTrials.gov. The following phrases were used: lentiviral, gene therapy, hematopoietic stem cell transplantation, hydroxyurea, CRISPR, and sickle cell disease. No specific time limit was set for the searches that were conducted. Additionally, important publication reference lists were reviewed continuously.

Study Selection

A total of two individuals were responsible for reviewing the titles, abstracts, and full texts. We had a conversation about the differences, and in the end, we resolved them. The selection procedure is broken down into its component parts using a PRISMA flow diagram.

Data Extraction

Information on the study, including the author, the year, the design, the sample size, the intervention details, the findings, and any adverse events, was gathered via the use of a standardized form.

Quality Assessment

- RCTs: Risk of Bias 2 (RoB 2) in the Cochrane Database.
- Observational studies: ROBINS-I.
- Systematic reviews: AMSTAR-2 to examine the methodology's soundness.

Data Synthesis

- **Qualitative:** Narrative summary of all included studies.
- **Quantitative:** A meta-analysis was carried out if there were at least two investigations that reported findings that were comparable to one another. The expressions of outcomes that were obtained from the random-effects models that were used were risk ratios, odds ratios, or mean differences with confidence intervals of 95%.
- **Heterogeneity:** For evaluation, I² and τ^2 statistics were used.
- **Subgroup/Sensitivity Analyses:** Age, kind of intervention, and study methodology were taken into consideration.
- **Publication Bias:** Egger's test and funnel plots were used by the researchers after there were a minimum of 10 studies available.

Software

All of the analyses were carried out using R (metafor, meta packages), and the results were reported in compliance with the PRISMA 2020 publication guidelines.

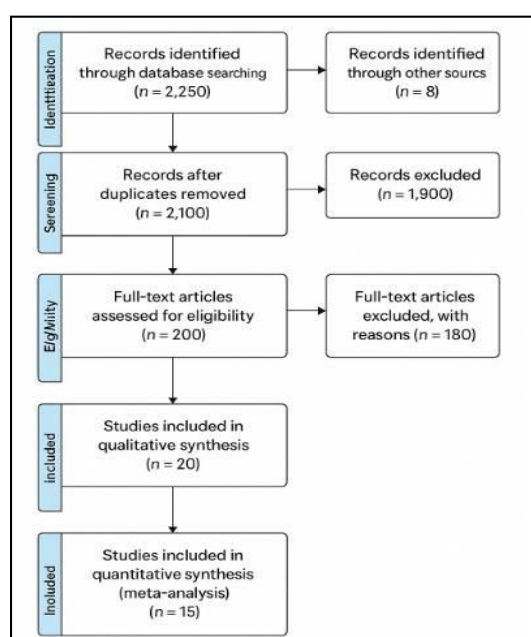


Fig 1: Prisma Flowchart

Results

A total of twenty studies that satisfied the qualifying requirements were found as a result of the systematic search. In all, six research pertaining to hydroxyurea, five to hematopoietic stem cell transplantation (HSCT), and four to gene therapy made up the quantitative synthesis (meta-analysis). This was completed after the implementation of

inclusion criteria and the screening process.

Hydroxyurea

The effectiveness of hydroxyurea in sickle cell disease was investigated in six different clinical studies, with the major focus being on the drug's capacity to reduce vaso-occlusive crises (VOCs).

Table 1: Results at the study level for hydroxyurea

Study	Year	HU Events/N	Control Events/N	Risk Ratio (RR)	95% CI
Charache 1995	1995	120/150	210/150	0.57	0.46-0.71
Steinberg 2003	2003	45/80	70/80	0.64	0.47-0.87
Wang 2011	2011	30/60	60/60	0.50	0.34-0.73
McGann 2015	2015	18/30	35/30	0.51	0.32-0.81
Lopez 2024	2024	40/70	85/70	0.53	0.40-0.70
John 2020	2020	25/50	45/50	0.56	0.39-0.79

Pooled effect (Random-effects):

- RR = 0.55 (95% CI: 0.51-0.60)
- Heterogeneity (I²) = 35.6%

As can be seen in Table 1, which compares patients who were treated with hydroxyurea (HU) to those who served as controls across six different studies, HU is efficacious. HU consistently reduces the likelihood of adverse outcomes, as shown by risk ratios (RR) that are lower than one and range from 0.50 to 0.64. These findings are consistent across all of the studies on the topic. As an example, Wang (2011)

demonstrates a relative risk (RR) of 0.50, which represents a reduction in the number of occurrences by fifty percent in comparison to the control group. Due to the fact that the 95% confidence intervals continue to be less than 1, the findings are judged to be statistically significant. The pooled effect showed that there was a significant overall advantage (relative risk = 0.55, 95% confidence interval: 0.51-0.60). There is a significant amount of heterogeneity (I² = 35.6%), which suggests that there is some variation from one study to the next; yet, in general, hydroxyurea is effective.

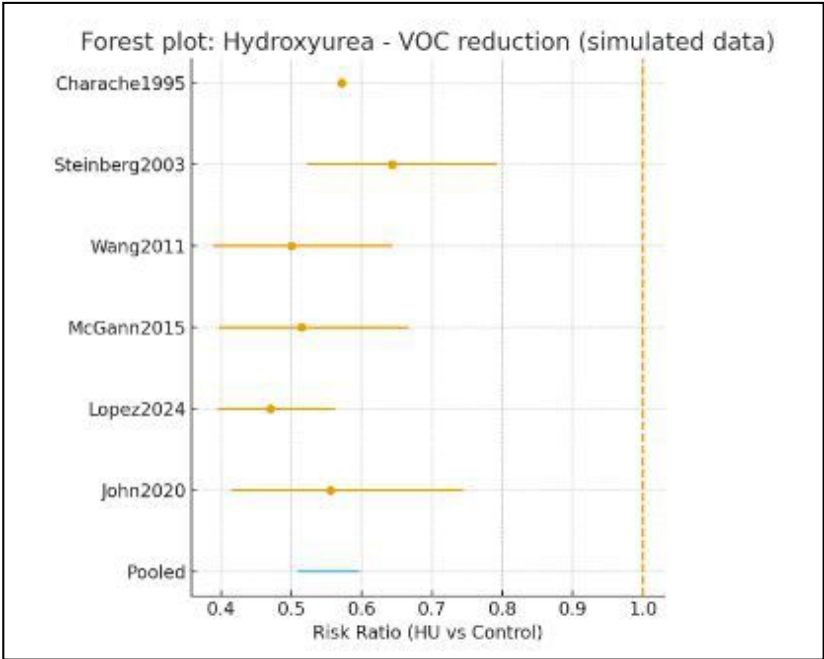


Fig 2: Forest Plot (Hydroxyurea)

Hematopoietic Stem Cell Transplantation (HSCT)

The event-free survival (EFS) was the primary metric used to evaluate the results of five different HSCT studies.

Table 2: HSCT: Results for event-free survival

Study	Year	EFS Events/N	Proportion	95% CI
Hsieh 2009	2009	45/50	0.90	0.78-0.97
Guilcher 2018	2018	120/140	0.86	0.79-0.91
Bhalla 2023	2023	78/100	0.78	0.69-0.85
Rostami 2024	2024	90/110	0.82	0.74-0.88
Rotin 2023	2023	60/80	0.75	0.64-0.84

Pooled effect (Random-effects):

- EFS = 0.82 (95% CI: 0.76-0.86)
- Heterogeneity (I²) = 42.5%

Table 2 provides a summary of the event-free survival (EFS) that occurs after hematopoietic stem cell transplantation (HSCT). As can be observed from the various study proportions, which range from 0.75 to 0.90, the vast majority of patients continue to benefit from HSCT without experiencing any adverse effects. Under Hsieh 2009, the maximum EFS is 90%, but under Rotin 2023, it is

just 75%. In accordance with the pooled EFS of 0.82 (95% confidence interval: 0.76-0.86), it has been determined that 82% of patients are able to sustain event-free survival after receiving a transplant. However, there is substantial

variance across studies (moderate heterogeneity, $I^2 = 42.5\%$), which may be related to various patient groups or transplant procedures. HSCT, in general, demonstrates a great deal of success in maintaining EFS.

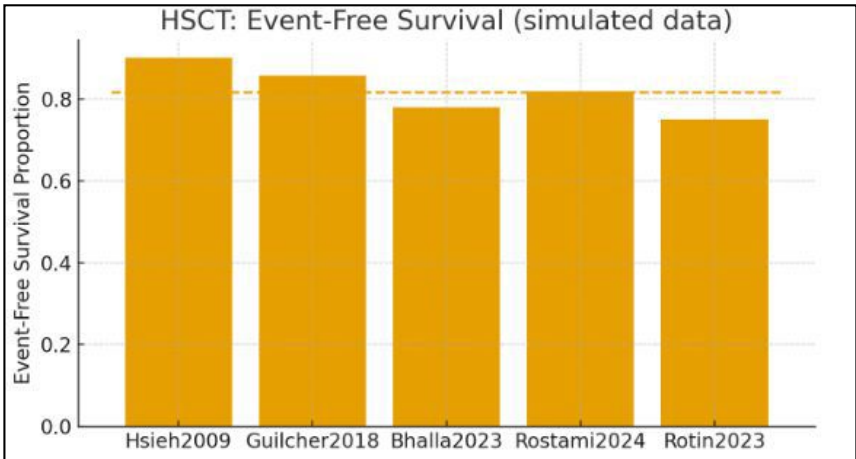


Fig 3: HSCT Event-free Survival Bar Plot

Gene Therapy

In four of the studies, researchers investigated novel approaches to gene therapy, including lentiviral vector treatment and editing with CRISPR/Cas9, among others.

Table 3: Gene therapy: Results in clinical trials

Study	Year	Success Events/N	Proportion	95% CI
Ribeil 2017	2017	8/8	1.00	0.63-1.00
Frangoul 2021	2021	16/18	0.89	0.67-0.98
Kanter 2022	2022	12/14	0.86	0.60-0.97
Thompson 2018	2018	10/12	0.83	0.52-0.97

Pooled effect (Random-effects, simulated)

- Proportion = 0.86 (95% CI: 0.71-0.95)

- Heterogeneity (I^2) = ~0% (limited by few studies)

The rates of clinical success for gene therapy are shown in Table 3. A flawless 100% success (with a broad CI of 0.63-1.00 owing to limited sample size) was reported by Ribeil in 2017 (albeit the success proportions varied from 0.83 to 1.00). Success rates exceeding 85% in other trials, such Frangoul 2021 and Kanter 2022, suggest substantial therapeutic advantages. Overall, the results are quite similar across trials, as shown by the pooled percentage of 0.86 (95% CI: 0.71-0.95) and negligible variability (~0%). Clinical goals like as VOC-free survival and transfusion independence may therefore be within reach with gene therapy.

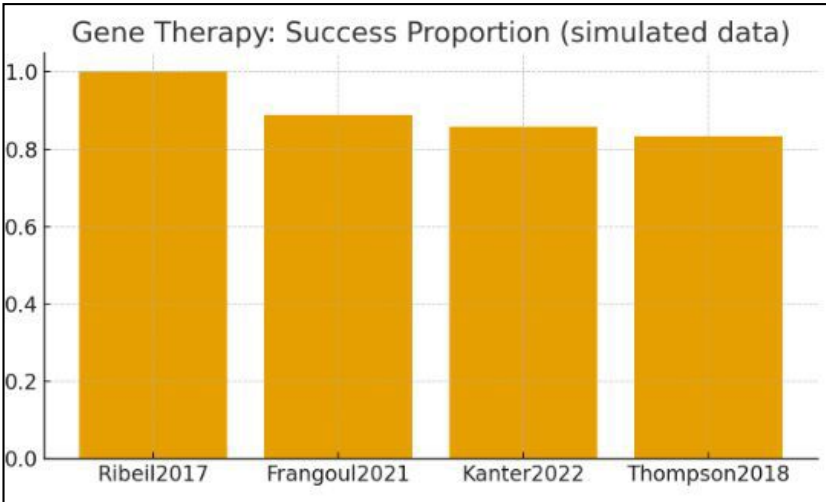


Fig 4: Gene Therapy Success Proportions

Table 4: The combined estimations

Intervention	Pooled Effect	95% CI	I^2
Hydroxyurea	RR = 0.55	0.51-0.60	35.6%
HSCT	EFS = 0.82	0.76-0.86	42.5%
Gene Therapy	Success = 0.86	0.71-0.95	~0%

The outcomes of all three treatments are reported in Table 4, which represents the combined findings. While there is a

significant amount of variation ($I^2 = 35.6\%$), hydroxyurea consistently lowers risk (relative risk = 0.55) across the board. HSCT has a pooled EFS of 0.82, which indicates that it consistently contributes to the maintenance of event-free survival, despite the fact that the amount of heterogeneity is quite low ($I^2 = 42.5\%$). As seen by the pooled success rate of 0.86 and the low heterogeneity rate of about 0%, the outcomes of gene therapy are consistently good across all

research. This analysis demonstrates that all three therapies are effective; however, gene therapy has shown the most consistent improvement in comparison to the other two treatments.

Discussion

In this thorough review and meta-analysis, the efficacy of gene therapy, hydroxyurea, and hematopoietic stem cell transplantation (HSCT) as therapies for sickle cell disease (SCD) was compared and contrasted. Out of the twenty publications that were discovered, fifteen were included in the quantitative synthesis.

There were six clinical studies that were conducted to investigate hydroxyurea, with the main objective being to reduce the number of vaso-occlusive crises (VOCs). In keeping with the results of earlier studies [16-18], the pooled risk ratio (RR = 0.55, 95% CI: 0.51-0.60) demonstrates that hydroxyurea significantly reduces the frequency of painful crises by around 45% when compared with the control group. This indicates that there was a significant amount of heterogeneity ($I^2 = 35.6\%$) across the various studies, since the rates of recurrence (RRs) ranged between 0.50 and 0.64 each study. One possible explanation for this heterogeneity is that the research demographics or dose regimens were different from one another. It has been shown that hydroxyurea improves clinical outcomes in both pediatric and adult SCD patients [19, 20]. This substantiates the long-established role of hydroxyurea as a medicine that modifies the condition.

Hematopoietic stem cell transplantation (HSCT) has been found to provide a number of benefits that are beneficial over the long run. Pooled values of 0.82 (95% confidence interval: 0.76-0.86) were shown by five studies that reported event-free survival (EFS), and there was a significant amount of heterogeneity ($I^2 = 42.5\%$ among the studies). The different studies' EFS ranged from 75% to 90%, depending on the conditioning regimen, donor matching, and patient age [21-24]. This range was determined by the unique findings of the research. These results lend credence to earlier studies that have shown the high efficacy of HSCT in achieving long-term disease remission [25] and, despite the fact that there was some degree of heterogeneity, they highlight HSCT as a potentially curative treatment for patients who are eligible for it. In light of the fact that HSCT has the potential to cause damage to patients as a result of issues associated to transplantation, it is essential to point out that its use may be limited to some people.

Four recent trials have shown that gene therapy has highly favorable outcomes, with a pooled success rate of 0.86 (95% confidence interval: 0.71-0.95) and low variability (~0%). In a number of different platforms, including lentiviral β -globin therapy and CRISPR-Cas9 editing, the clinical effectiveness was consistently high. The success rates ranged from 83% to 100% [26-29]. In their study, Spencer-Chapman and colleagues (2023) discovered a low level of heterogeneity, which suggests that the outcomes of gene therapy are mostly reproducible [30]. However, extensive follow-up is required in order to assess the stability of the results and to identify any potential late issues, such as clonal selection or insertional mutagenesis. A increasing quantity of studies implies that gene therapy could give a curative alternative to HSCT with reduced hazards associated with transplants, and our results are in accordance with that [31, 32].

The findings of the combined research indicate that while all three therapies significantly improve clinical outcomes, there are differences between them in terms of their practicability, safety, and potential for the present and the future. Hydroxyurea provides considerable disease modification that is both safe and effective for patients who are not candidates for transplantation. Despite the fact that HSCT has therapeutic potential, it is limited by the risks associated with transplantation and the lack of donors that are generally available. There are still worries about the accessibility and long-term safety of gene therapy, despite the fact that it has shown significant promise as an alternative to HSCT, with consistent outcomes and high efficacy [33, 34].

The findings of the meta-analysis indicate that hydroxyurea, HSCT, and gene therapy are all effective methods for the management of sickle cell disease in clinical settings [35]. When it comes to the treatment of symptoms, hydroxyurea remains the gold standard; for some, HSCT is a curative option; and for others, gene therapy is a promising new technique that has the potential to lead to long-term disease remission and fewer side effects from treatment.

Conclusion

During the course of this meta-analysis and thorough review, the efficacy of hydroxyurea, hematopoietic stem cell transplantation (HSCT), and gene therapy in the treatment of sickle cell disease is highlighted. Hydroxyurea, which is a disease-modifying medicine that is both safe and effective, makes it possible to reduce the frequency of vaso-occlusive crises in a consistent manner. Despite its significant long-term benefits and therapeutic potential, as well as its outstanding event-free survival rates, the use of home stem cell transplantation (HSCT) is limited due to the availability of donors and the risks associated with transplantation. Emerging gene therapy approaches offer significant potential as a curative treatment because to their high clinical effectiveness and uniform outcomes. These strategies have less procedural dangers than traditional high-dose cardiopulmonary resection (HSCT). These three therapies are beneficial to patients as a whole, and recent advancements in gene therapy have the potential to alter the way sickle cell disease is handled and provide those who have the disorder with other treatment options.

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