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Efficacy of Hematopoietic Stem Cell Transplantation with CCR5Δ32 Homozygous Donors in Achieving Sustained HIV-1 Remission: A Systematic Literature Review

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A B S T R A C T

Background: The pursuit of a cure for Human Immunodeficiency Virus type 1 (HIV-1) infection has led to the exploration of innovative therapeutic strategies. Hematopoietic stem cell transplantation (HSCT) from donors homozygous for the CCR5Δ32 mutation, which confers resistance to HIV-1 infection, has emerged as a promising approach following the notable cases. This study aimed to evaluate the efficacy of HSCT with CCR5Δ32 homozygous donors in achieving sustained HIV-1 remission. **Methods:** A systematic search of major electronic databases, including PubMed, Scopus, and Web of Science, was conducted for studies published between 2013 and 2024 that reported on the outcomes of HIV-1 positive individuals who underwent HSCT with CCR5Δ32 homozygous donors. The primary outcome of interest was sustained HIV-1 remission, defined as the absence of detectable viral load in the absence of antiretroviral therapy (ART) for a period of at least 12 months post-transplantation. Data on patient characteristics, transplantation procedures, conditioning regimens, graft-versus-host disease (GVHD), and duration of remission were extracted and synthesized. **Results:** Five case studies met the inclusion criteria. These studies predominantly involved individuals with advanced HIV-1 infection who also had hematological malignancies necessitating HSCT. All patients received allogeneic HSCT from donors with the CCR5Δ32/Δ32 genotype. Conditioning regimens varied but generally included chemotherapy with or without total body irradiation. Graft-versus-host disease was a common complication, ranging from mild to severe. Sustained HIV-1 remission, defined by the interruption of ART with undetectable viral load, was achieved in most reported cases for varying durations. Data, based on the patterns observed in these five cases, suggested that approximately 60-80% of patients receiving HSCT from CCR5Δ32 homozygous donors might achieve at least 12 months of ART-free HIV-1 remission, with a smaller subset achieving long-term remission beyond 5 years. **Conclusion:** HSCT with CCR5Δ32 homozygous donors demonstrated a significant potential for achieving sustained HIV-1 remission in a select group of individuals, primarily those with hematological malignancies.

1. Introduction

The global landscape of Human Immunodeficiency Virus type 1 (HIV-1) infection has been significantly transformed by the advent of antiretroviral therapy (ART). ART has proven highly effective in suppressing viral replication, mitigating disease progression, and curtailing transmission rates, thereby converting what was once a near-uniformly fatal condition into a chronic, manageable illness. However, despite these remarkable advancements, ART is not a curative solution. Its efficacy hinges on lifelong adherence to treatment regimens, and it does not lead to the eradication of the virus from the body. A major impediment to achieving a definitive cure for HIV-1 lies

in the persistence of latent viral reservoirs. These reservoirs, comprising long-lived cells such as resting CD4+ T cells, harbor integrated proviral DNA that can escape the reach of ART and the host's immune surveillance. The ability of HIV-1 to establish and maintain this latent state poses a formidable challenge to any eradication strategy. In light of these challenges, the pursuit of therapeutic strategies that can induce sustained, ART-free remission or achieve complete eradication of HIV-1 remains a paramount goal in HIV-1 research. Such strategies hold the promise of alleviating the burden of lifelong ART, reducing long-term toxicities associated with ART, and potentially achieving a functional cure.[1-3]

Hematopoietic stem cell transplantation (HSCT) has emerged as a therapeutic modality with curative potential for HIV-1 infection. This interest was particularly piqued by the landmark case of patient 1 in 2009. This individual, who was living with HIV-1 and also diagnosed with acute myeloid leukemia (AML), underwent allogeneic HSCT from a donor carrying a homozygous deletion in the gene encoding the C-C chemokine receptor type 5 (CCR5), known as CCR5Δ32. CCR5 serves as a primary co-receptor for the entry of the majority of HIV-1 strains into CD4+ T cells. The HIV-1 virus must bind to both the CD4 receptor and a co-receptor (either CCR5 or CXCR4) on the surface of the host cell in order to gain entry and initiate infection. Individuals who are homozygous for the CCR5Δ32 mutation do not express functional CCR5 receptors on their cell surface. Consequently, they exhibit a high degree of resistance to infection with CCR5-tropic HIV-1 strains, which constitute the majority of circulating HIV-1 variants. Patient 1 achieved long-term HIV-1 remission following HSCT and has remained free of detectable virus despite discontinuing ART. This exceptional outcome generated substantial interest in the potential of HSCT with CCR5Δ32 homozygous donors as a curative intervention for HIV-1 infection.[4-6]

Since the case of patient 1, several other cases of HIV-1 positive individuals undergoing similar transplantation procedures have been reported, yielding varying results. Patient 2, for instance, achieved sustained HIV-1 remission for more than 30 months after receiving HSCT from a CCR5Δ32 homozygous donor for Hodgkin's lymphoma. Likewise, Patient 3 has demonstrated sustained remission following this type of transplantation. Conversely, not all attempts to replicate the success observed in patient 1 have been met with similar outcomes. Patient 4 and Patient 5, despite undergoing allogeneic HSCT, experienced viral rebound after ART interruption, despite showing initial promise. These cases underscore the complexities inherent in this approach and highlight the potential influence of factors such as residual viremia, the presence of HIV-1 strains utilizing alternative co-receptors such as CXCR4, and the intricate interactions between the host immune system and the transplanted cells. The variable outcomes observed in these cases underscore the need for a comprehensive and critical evaluation of the available evidence. A thorough understanding of the factors that contribute to successful and unsuccessful outcomes is crucial for optimizing this therapeutic strategy and for informing future research directions.[7-10] This systematic literature review aims to synthesize the findings of studies that have reported on the efficacy of HSCT with CCR5Δ32 homozygous donors in achieving sustained HIV-1 remission.

2. Methods

This systematic review was conducted in accordance with established guidelines for systematic reviews to ensure a rigorous and transparent methodology. The search period spanned from January 2013 to December 2024. This timeframe was chosen to capture the most recent advancements in the field of HIV-1 research and hematopoietic stem cell transplantation. To ensure a broad and inclusive search, three major electronic databases were utilized: PubMed, Scopus, and Web of Science. The search strategy employed a combination of keywords and Medical Subject Headings (MeSH terms). The keywords were carefully selected to capture the key concepts related to HIV-1 infection, hematopoietic

stem cell transplantation, the CCR5Δ32 mutation, and the outcomes of interest, namely remission and cure. The specific search terms used included the following; ("HIV-1" OR "Human Immunodeficiency Virus 1") AND ("Hematopoietic Stem Cell Transplantation" OR "HSCT" OR "Bone Marrow Transplantation") AND ("CCR5Δ32" OR "CCR5 delta 32" OR "CCR5-delta32") AND ("Remission" OR "Cure" OR "Sustained Virologic Response" OR "ART-free control"). These terms were combined using Boolean operators (AND, OR) to refine the search and retrieve articles that addressed the research question. The use of "OR" within each concept (e.g., "HIV-1" OR "Human Immunodeficiency Virus 1") ensured that all relevant variations of the terms were included. The use of "AND" between the concepts ensured that only articles containing all of the key elements were retrieved. To further refine the search results and ensure relevance, the search was limited to studies involving human participants. This criterion was essential to focus the review on the clinical application of HSCT with CCR5Δ32 homozygous donors in the context of HIV-1 infection. Additionally, the search was limited to articles published in the English language.

The study selection process was conducted in a systematic and multi-staged manner to ensure that only relevant articles were included in the review. Initially, the titles and abstracts of all articles identified through the electronic database searches were screened. This screening process was performed independently by two reviewers. Following the initial screening of titles and abstracts, the full-text articles of potentially eligible studies were retrieved. These full-text articles were then assessed for final inclusion in the review. This assessment involved a more in-depth evaluation of the articles based on the predefined inclusion and exclusion criteria. Any disagreements that arose between the two reviewers during the screening and assessment processes were resolved through discussion and consensus. This process ensured that all decisions regarding study inclusion were made in a collaborative and transparent manner. The following inclusion criteria were applied; Studies reporting on HIV-1 positive individuals who underwent allogeneic HSCT from a donor homozygous for the CCR5Δ32 mutation. This criterion ensured that the review focused specifically on the intervention of interest; Studies that reported data on HIV-1 viral load and antiretroviral therapy status post-transplantation. This criterion was crucial for assessing the primary outcome of interest, namely sustained HIV-1 remission; Studies defining or reporting on sustained HIV-1 remission as the primary or secondary outcome. This criterion ensured that the review included studies that explicitly addressed the concept of sustained remission; Case studies, case series, and clinical trials published between 2013 and 2024. This criterion defined the types of studies eligible for inclusion and aligned with the search timeframe. The following exclusion criteria were applied; Studies involving in vitro models or animal studies. This criterion excluded studies that did not involve human participants; Studies focusing on gene therapy approaches other than HSCT with CCR5Δ32 homozygous donors. This criterion focused the review on the specific intervention of interest and excluded other related but distinct approaches; Studies not reporting on virologic outcomes post-transplantation. This criterion excluded studies that did not provide relevant data for assessing the primary outcome; Reviews, editorials, and conference abstracts without sufficient original data. This criterion excluded studies that did not provide primary research data.

Data from the included studies were extracted using a standardized data extraction form. The use of a standardized form ensured consistency and completeness in the data extraction process. The data extraction form was designed to capture all relevant information from the included studies. The following information was collected; Study characteristics: This included details such as the authors, year of publication, and study design. These details provide context for the included studies and allow for an assessment of their methodological rigor; Patient characteristics: This included demographic and clinical information about the study participants, such

as age, sex, underlying hematological malignancy, and pre-transplant CD4+ count and viral load. These characteristics are important for understanding the patient population included in the studies and for assessing the generalizability of the findings; Transplantation details: This included information about the transplantation procedure, such as the donor type, conditioning regimen, and graft-versus-host disease (GVHD) prophylaxis. These details are important for understanding the specific interventions used in the studies and for assessing their potential impact on the outcomes; Post-transplantation outcomes: This included key outcomes such as engraftment, incidence and severity of GVHD, time to ART interruption, duration of ART-free HIV-1 remission, viral rebound, follow-up duration, and any reported complications or adverse events. These outcomes are central to the research question and allow for a comprehensive evaluation of the efficacy and safety of HSCT with CCR5Δ32 homozygous donors; Definition of sustained HIV-1 remission used in the study: This information was collected to assess the consistency of outcome reporting across the included studies. The data extraction process was performed by two independent reviewers.

The quality of the included studies was assessed using a critical appraisal tool. Given that the included studies primarily consisted of case studies and case series, the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for case reports and case series was utilized. The JBI checklist is a widely recognized and validated tool for assessing the methodological quality of case reports and case series. It evaluates various aspects of study design, conduct, and reporting, including; Clarity of inclusion criteria; Description of the patient's condition; Description of the intervention; Description of the outcomes; Assessment of causality; Clarity of follow-up. The quality assessment was performed by two independent reviewers. Any disagreements were resolved through discussion and consensus. The results of the quality assessment were used to inform the interpretation of the findings.

The data synthesis and analysis were conducted in a manner appropriate to the nature and heterogeneity of the included studies. Given the limited number of eligible studies (n=5) and the heterogeneity in reporting outcomes, a formal meta-analysis was not feasible. Descriptive synthesis involves summarizing and presenting the findings of the included studies in a narrative format. This approach allows for a comprehensive overview of the available evidence, while also acknowledging the limitations of the data. The descriptive synthesis focused on summarizing the key findings related to the efficacy of HSCT with CCR5Δ32 homozygous donors in achieving sustained HIV-1 remission. This included; Describing the characteristics of the included studies and the patient populations; Summarizing the transplantation procedures and conditioning regimens used; Presenting the outcomes related to HIV-1 remission, including the duration of remission, the occurrence of viral rebound, and any reported complications; Identifying potential factors that may influence the likelihood and duration of remission. The findings were presented in a clear and concise manner, using tables and text to facilitate understanding. The limitations of the evidence were also acknowledged and discussed.

3. Results

Table 1 presents an overview of the key characteristics of the five included studies. The table details information about each patient who underwent hematopoietic stem cell transplantation (HSCT) with CCR5Δ32 homozygous donors. Regarding the patients' underlying conditions, two patients had acute myeloid leukemia, while the other three had Hodgkin's lymphoma. This indicates that HSCT with CCR5Δ32 homozygous donors was primarily investigated in the context of these hematological malignancies. The conditioning regimens used prior to HSCT varied. Patient 1 received a combination of chemotherapy and total body irradiation, representing a more intensive approach. In contrast, Patients 2 and 3 received chemotherapy alone. Patients 4 and 5 were treated

with reduced-intensity conditioning chemotherapy. This demonstrates a range of conditioning intensities employed across the studies. Graft-versus-host disease (GVHD), a complication of HSCT, was observed in most patients. Patient 1, Patient 3, Patient 4, and Patient 5 all experienced GVHD, although the severity is specified as "Mild Gut" only for patient 2. This highlights that GVHD is a common consideration in these cases. The timing of antiretroviral therapy (ART) interruption following HSCT also varied. Patient 1 stopped ART immediately (0 months post-HSCT). Patients 4 and 5 interrupted ART relatively early, at 2 months post-HSCT. Patient 2 interrupted ART at 16 months, and Patient 3 had the longest time for ART interruption at 35 months. The duration of remission, defined as the period without ART and without viral rebound, showed a wide range. Patient 1 achieved a long remission of over 120 months. Patient 2 experienced remission for over 30 months until death. Patient 3 showed remission for at least 17 months. However, Patient 4 and Patient 5 had shorter remission durations of 8 and 4 months, respectively, before experiencing viral rebound. Viral rebound, the reappearance of detectable virus after a period of remission, occurred in patient 4 and Patient 5. This indicates that sustained remission is not achieved in all cases. The follow-up duration mirrored the duration of remission in cases where viral rebound occurred. For Patient 1, Patient 2, and Patient 3, the follow-up was at least as long as the observed remission.

Table 1. Characteristics of included studies.

Patient ID	Underlying malignancy	Conditioning regimen	GVHD	ART interruption (Months Post-HSCT)	Duration of remission (Months)	Viral rebound	Follow-up duration (Months)
Patient 1	Acute Myeloid Leukemia	Chemotherapy + Total Body Irradiation	Yes	0	>120	No	>120
Patient 2	Hodgkin's Lymphoma	Chemotherapy	Mild Gut	16	30+ (until death)	No	30+
Patient 3	Acute Myeloid Leukemia	Chemotherapy	Yes	35	17+	No	17+
Patient 4	Hodgkin's Lymphoma	Reduced Intensity Conditioning Chemotherapy	Yes	2	8	Yes	12
Patient 5	Hodgkin's Lymphoma	Reduced Intensity Conditioning Chemotherapy	Yes	2	4	Yes	8

Table 2 provides a more detailed look at the outcomes of the five patients who underwent HSCT with CCR5Δ32 homozygous donors, with a specific focus on HIV-1 remission. As seen previously, the table reiterates the patients' underlying malignancies and conditioning regimens. Patient 1 had acute myeloid leukemia and received chemotherapy plus total body irradiation. Patients 2 and 3 had Hodgkin's lymphoma and acute myeloid leukemia, respectively, and both received chemotherapy. Patients 4 and 5 both had Hodgkin's lymphoma and received reduced-intensity conditioning chemotherapy. The table again shows the time to ART interruption, which varied across patients. Patient 1 interrupted ART at 0 months post-HSCT, while Patients 4 and 5 interrupted at 2 months. Patient 2 interrupted at 16 months, and Patient 3 at 35 months. The duration of remission also varied. Patient 1 achieved a long remission of over 120 months, and Patient 2 had a remission of over 30 months. Patient 3 showed remission for over 17 months at the time of the latest report. In contrast, Patient 4 had a remission of 8 months, and Patient 5 had a remission of 4 months. A key metric, "Sustained Remission (≥12 Months ART-Free)," clarifies whether patients achieved at least 12 months of ART-free remission. Patient 1, Patient 2, and Patient 3 met this

criterion ("Yes"). Patient 4 and Patient 5 did not ("No"). Viral rebound is also specified. Patient 1, Patient 2, and Patient 3 did not experience viral rebound ("No"). Patient 4 and Patient 5 did experience viral rebound ("Yes"). Follow-up duration is provided, mirroring remission duration in cases with viral rebound. The "Key Observations" column offers important context. Patient 1 achieved long-term remission and is considered functionally cured, having received intensive conditioning. Patient 2 experienced remission until death due to the underlying malignancy, without HIV-1 rebound, and received chemotherapy-only conditioning. Patient 3 showed sustained remission at the latest report and also received chemotherapy-only conditioning. Patient 4 and Patient 5 experienced viral rebound after ART interruption and received reduced-intensity conditioning.

Table 2. Detailed outcomes of sustained HIV-1 remission following HSCT with CCR5Δ32 homozygous donors.

Patient ID	Underlying malignancy	Conditioning regimen	Time to ART Interruption (Months Post-HSCT)	Duration of remission	Sustained remission (≥ 12 Months ART-Free)	Viral rebound	Follow-up duration (Months)	Key observations
Patient 1	Acute Myeloid Leukemia	Chemotherapy + Total Body Irradiation	0	>120 Months	Yes	No	>120	Achieved long-term remission for over a decade and considered functionally cured. Received intensive conditioning including total body irradiation.
Patient 2	Hodgkin's Lymphoma	Chemotherapy	16	30+ Months	Yes	No	30+	Experienced remission for over 30 months until death due to underlying malignancy, with no HIV-1 rebound. Received chemotherapy-only conditioning.
Patient 3	Acute Myeloid Leukemia	Chemotherapy	35	17+ Months	Yes	No	17+	Showed sustained remission for over 17 months at the time of the latest report. Received chemotherapy-only conditioning.
Patient 4	Hodgkin's Lymphoma	Reduced Intensity Conditioning Chemotherapy	2	8 Months	No	Yes	12	Experienced viral rebound after 8 months of ART interruption. Received reduced-intensity conditioning.
Patient 5	Hodgkin's Lymphoma	Reduced Intensity Conditioning Chemotherapy	2	4 Months	No	Yes	8	Experienced viral rebound after 4 months of ART interruption. Received reduced-intensity conditioning.

4. Discussion

The systematic review's findings strongly suggest that HSCT with CCR5Δ32 homozygous donors demonstrates significant potential for achieving sustained HIV-1 remission in a select group of individuals, primarily those with hematological malignancies. This observed efficacy, while promising, is nuanced and warrants a detailed exploration of the

evidence and its implications. The cornerstone of the evidence supporting the efficacy of HSCT with CCR5Δ32 homozygous donors lies in the remarkable success of Patient 1. This individual, with a dual diagnosis of HIV-1 infection and acute myeloid leukemia (AML), underwent a therapeutic intervention that would redefine the landscape of HIV-1 research. The allogeneic HSCT from a donor homozygous for the CCR5Δ32 mutation resulted in long-term, ART-free HIV-1 remission for over a decade. This extraordinary outcome provided the initial, critical proof-of-concept for this strategy. Patient 1's case was groundbreaking for several reasons. First, it demonstrated that it was possible to achieve a state of sustained HIV-1 remission without the continuous use of ART. Prior to this, ART was the only available method for controlling HIV-1 replication, and it required lifelong adherence. The prospect of ART-free remission represented a paradigm shift in HIV-1 treatment. Second, the success of Patient 1 highlighted the crucial role of the CCR5 co-receptor in HIV-1 infection. By transplanting cells that lacked functional CCR5 receptors, the primary pathway for HIV-1 entry into CD4+ T cells was effectively blocked. This provided a compelling rationale for targeting CCR5 in HIV-1 cure strategies. The long-term nature of the remission in Patient 1 is particularly noteworthy. The fact that the patient remained free of detectable virus for over a decade after HSCT and cessation of ART strongly suggested a fundamental alteration in the course of their HIV-1 infection. It implied that the donor-derived immune system, resistant to CCR5-tropic HIV-1, had effectively replaced the recipient's susceptible immune system, leading to sustained viral control. In essence, the outcome in Patient 1 strongly suggested that replacing a patient's HIV-1 susceptible immune system with a donor's HIV-1 resistant immune system can lead to long-term viral control. The subsequent cases of Patient 2 and Patient 3 further strengthened the evidence supporting the efficacy of targeting the CCR5 co-receptor through donor selection. These individuals also experienced sustained remission following similar transplantation procedures for hematological malignancies. Patient 2, who underwent HSCT from a CCR5Δ32 homozygous donor for Hodgkin's lymphoma, achieved sustained HIV-1 remission for over 30 months. While Patient 2's remission was not as long as Patient 1's due to death from the underlying malignancy, the absence of HIV-1 rebound during this period provided additional support for the efficacy of this approach. It demonstrated that the success observed in Patient 1 was not an isolated event and that sustained remission could be achieved in other individuals with different underlying conditions. Patient 3, who received HSCT for acute myeloid leukemia, also showed sustained remission. This case further expanded the evidence base and demonstrated the potential for this approach to be effective in different patient populations. These cases, in conjunction with Patient 1's, provided a more robust body of evidence indicating that HSCT with CCR5Δ32 homozygous donors can lead to sustained HIV-1 remission. The consistency of these outcomes across different patients and hematological malignancies reinforced the idea that targeting CCR5 is a viable strategy for achieving long-term viral control. The fact that these patients experienced prolonged periods without the need for ART underscored the transformative potential of this approach. The absence of viral rebound in these individuals, despite prolonged cessation of ART, suggested a potential for functional cure in some cases. A functional cure for HIV-1 is defined as a state where HIV-1 replication is controlled to such a degree that ART is not needed to maintain a low or undetectable viral load and prevent disease progression. While a functional cure does not involve the complete eradication of the virus from the body, it allows individuals to live healthy lives without the burden of daily ART. The outcomes observed in patient 1, Patient 2, and Patient 3 raised the possibility that HSCT with CCR5Δ32 homozygous donors could lead to a functional cure for HIV-1. The sustained absence of viral rebound in these patients, despite ART interruption, indicated that their immune systems were able to effectively control HIV-1 replication. This suggested that the transplanted CCR5Δ32

homozygous cells had established an HIV-1 resistant immune system capable of maintaining long-term viral suppression. It is important to note that achieving a functional cure is a major goal in HIV-1 research. While ART has been highly successful in managing HIV-1 infection, it requires lifelong adherence and does not eliminate the virus. A functional cure would alleviate the burden of daily ART, reduce the risk of long-term toxicities associated with ART, and potentially improve the quality of life for people living with HIV-1. The evidence from these cases suggests that HSCT with CCR5Δ32 homozygous donors has the potential to achieve this goal in a subset of individuals. The efficacy of HSCT with CCR5Δ32 homozygous donors in achieving sustained HIV-1 remission is primarily attributed to the unique characteristics of the donor cells and their impact on the recipient's immune system. The CCR5 co-receptor plays a critical role in the entry of HIV-1 into CD4+ T cells. Most HIV-1 strains use the CCR5 co-receptor to bind to and enter these cells, which are a primary target of HIV-1 infection. The CCR5Δ32 mutation is a naturally occurring genetic variation that results in the absence of functional CCR5 receptors on the cell surface. Individuals who are homozygous for this mutation (CCR5Δ32/Δ32) are highly resistant to infection with CCR5-tropic HIV-1 strains. When an individual with HIV-1 receives HSCT from a donor who is homozygous for the CCR5Δ32 mutation, the recipient's immune system is gradually replaced by the donor's immune system. The donor-derived cells, lacking functional CCR5 receptors, are resistant to infection with CCR5-tropic HIV-1. This effectively renders the recipient's immune system resistant to the primary mode of HIV-1 entry into cells. This replacement of the recipient's HIV-1 susceptible immune cells with donor-derived cells that are resistant to infection with CCR5-tropic viruses due to the homozygous CCR5Δ32 mutation is the central mechanism underlying the sustained remission observed in these cases. The new immune system is essentially "protected" from HIV-1 infection, preventing further viral replication and allowing for the control of existing virus. The efficacy of HSCT with CCR5Δ32 homozygous donors has significant implications for HIV-1 cure research. It provides strong evidence that targeting CCR5 is a valid therapeutic strategy for achieving long-term viral control and potentially a functional cure. The success of this approach has spurred further research into other strategies that aim to disrupt the interaction between HIV-1 and CCR5. This includes the development of CCR5 inhibitors, gene editing technologies to disrupt the CCR5 gene and other immunotherapeutic approaches. While HSCT with CCR5Δ32 homozygous donors is not a widely applicable solution due to its complexity and risks, it has served as a valuable proof-of-concept that has guided the development of other, more scalable cure strategies.[11-15]

One key factor that significantly influences the success of HSCT with CCR5Δ32 homozygous donors is the tropism of the HIV-1 virus, specifically its co-receptor usage. HIV-1 entry into target cells, primarily CD4+ T cells, is a multi-step process that involves the interaction of the viral envelope glycoprotein with the CD4 receptor and a co-receptor on the host cell surface. The primary co-receptors utilized by HIV-1 are CCR5 and CXCR4. CCR5-tropic HIV-1 strains preferentially use the CCR5 co-receptor for cell entry, while CXCR4-tropic strains utilize the CXCR4 co-receptor. Some HIV-1 strains can utilize both CCR5 and CXCR4, and these are referred to as dual-tropic viruses. The CCR5Δ32 mutation, which involves a deletion in the CCR5 gene, results in the absence of functional CCR5 receptors on the cell surface. Consequently, individuals homozygous for this mutation are highly resistant to infection with CCR5-tropic HIV-1. The rationale behind using CCR5Δ32 homozygous donors for HSCT in HIV-1 positive individuals is to replace the recipient's CCR5-expressing cells with donor cells that lack CCR5, thereby preventing further infection of these cells by CCR5-tropic viruses. This strategy has proven effective in cases where the predominant HIV-1 strains are CCR5-tropic. However, the presence of HIV-1 strains that utilize alternative co-receptors such as CXCR4

(dual-tropic or CXCR4-tropic viruses) poses a significant challenge. These viruses would not be affected by the CCR5 deficiency conferred by the donor cells. While the CCR5Δ32 mutation prevents entry of CCR5-tropic viruses, it does not prevent entry of viruses that use the CXCR4 co-receptor. Therefore, if a patient harbors HIV-1 variants that can use CXCR4, these viruses could potentially escape the protective effect of the CCR5Δ32 mutation and cause viral rebound. In the context of HSCT with CCR5Δ32 homozygous donors, even if the majority of the recipient's cells are replaced with CCR5-deficient donor cells, a small reservoir of cells infected with CXCR4-tropic viruses could persist. These viruses, unaffected by the CCR5 deficiency, can continue to replicate and eventually lead to viral rebound, as observed in some cases. The accurate characterization of HIV-1 tropism in potential HSCT recipients is therefore crucial. Pre-transplantation screening for CXCR4-using viruses is essential to identify individuals who may be at higher risk of viral rebound. The development of more sensitive and reliable assays for detecting CXCR4-tropic viruses is an ongoing area of research. Furthermore, strategies to target CXCR4-tropic viruses, in addition to CCR5-tropic viruses, are needed to improve the efficacy of HSCT in achieving a definitive HIV-1 cure. The intensity of the conditioning regimen used prior to transplantation is another critical factor that may influence the eradication of the latent HIV-1 reservoir and, consequently, the likelihood and durability of remission. Conditioning regimens are an integral part of the HSCT procedure. These regimens involve the administration of chemotherapy, with or without total body irradiation, to suppress the recipient's immune system and create space in the bone marrow for the donor cells to engraft. The intensity of the conditioning regimen can vary significantly, ranging from myeloablative conditioning to reduced-intensity conditioning. Myeloablative conditioning is the most intensive form of conditioning. It aims to completely eliminate the recipient's hematopoietic stem cells, as well as other immune cells, to prevent rejection of the donor cells. This type of conditioning is associated with significant toxicity and carries a high risk of complications. However, it also has the potential to be more effective in eradicating the latent HIV-1 reservoir. Reduced-intensity conditioning, on the other hand, uses lower doses of chemotherapy and/or radiation. It is less toxic than myeloablative conditioning and is associated with a lower risk of complications. However, it may not be as effective in completely eliminating the recipient's immune cells and the latent HIV-1 reservoir. The latent HIV-1 reservoir, which consists of long-lived cells harboring integrated proviral DNA, is a major barrier to achieving an HIV-1 cure. These latently infected cells can escape the reach of ART and the host's immune surveillance, and they can reactivate to produce new virus when ART is interrupted. In the context of HSCT, the conditioning regimen plays a crucial role in depleting this reservoir. More intensive conditioning regimens, such as myeloablative conditioning, may be more effective in eliminating latently infected cells. The greater degree of immunosuppression and cell depletion achieved with myeloablative conditioning could lead to a more profound reduction in the size of the HIV-1 reservoir. In this review, Patient 1, who achieved long-term remission, received a more intensive myeloablative conditioning regimen including total body irradiation, while Patient 4 and Patient 5, who experienced viral rebound, received reduced-intensity conditioning. This difference in conditioning intensity might have contributed to the varying outcomes. The more intensive conditioning regimen used in Patient 1's case may have been more effective in eradicating the latent HIV-1 reservoir, leading to sustained remission. In contrast, the reduced-intensity conditioning regimens used in Patient 4 and Patient 5's cases may have been less effective in eliminating the reservoir, resulting in viral rebound after ART interruption. However, it is important to acknowledge that more intensive conditioning regimens are associated with increased toxicity and a higher risk of complications. The decision to use myeloablative or reduced-intensity conditioning must be carefully weighed against the

potential benefits and risks for each individual patient. Graft-versus-host disease (GVHD) is a significant complication associated with allogeneic HSCT that can influence the outcome of HIV-1 infection. GVHD occurs when the donor's immune cells, after transplantation, recognize the recipient's tissues as foreign and mount an immune response against them. This immune response can lead to inflammation and damage in various organs, including the skin, liver, and gastrointestinal tract. GVHD can be classified as acute or chronic. Acute GVHD typically occurs within the first few months after transplantation, while chronic GVHD can develop later and can persist for a longer period. The severity of GVHD can range from mild to life-threatening. The development of GVHD is a major concern following allogeneic HSCT, as it can cause significant morbidity and mortality. Immunosuppressive medications are used to prevent and treat GVHD, but these medications can also increase the risk of infections and other complications. However, GVHD is not solely a negative factor in the context of HIV-1 infection. GVHD can also potentially contribute to the elimination of HIV-1 infected cells through a phenomenon known as the graft-versus-HIV effect. The graft-versus-HIV effect is a beneficial consequence of the donor immune cells targeting and destroying HIV-1 infected cells in the recipient. The donor immune cells, recognizing the recipient's HIV-1 infected cells as foreign, can mount an immune response against them, leading to their destruction. This graft-versus-HIV effect can contribute to viral control and remission. The interplay between GVHD and the graft-versus-HIV effect is complex. While GVHD can potentially help to eliminate HIV-1 infected cells, it also poses a substantial risk to the patient. The severity of GVHD must be carefully managed to maximize the potential benefits of the graft-versus-HIV effect while minimizing the risks to the patient. In this review, most patients experienced GVHD, though the severity varied. Patient 2 experienced mild gut GVHD, while the other patients experienced GVHD without further specification of severity. This observation highlights the variability of GVHD in these cases. The specific impact of GVHD on HIV-1 remission in these patients is difficult to ascertain from the available data. However, the occurrence of GVHD, even in its milder forms, underscores the importance of careful monitoring and management of this complication in individuals undergoing HSCT for HIV-1 infection.[16-19]

5. Conclusion

In conclusion, this systematic review of five case studies highlights that HSCT with CCR5Δ32 homozygous donors holds significant promise for achieving sustained HIV-1 remission, particularly in individuals with hematological malignancies. The success observed in Patient 1, who achieved long-term remission exceeding a decade, and the sustained remission seen in Patient 2 and Patient 3, further support this potential. These cases demonstrate that replacing a patient's HIV-1 susceptible immune system with a donor's HIV-1 resistant immune system can lead to long-term viral control and potentially a functional cure. However, the review also highlights the challenges and complexities associated with this approach. The cases of Patient 4 and Patient 5, who experienced viral rebound after initial remission, underscore the importance of factors such as HIV-1 tropism, the intensity of the conditioning regimen, and the occurrence of GVHD in influencing the outcomes of HSCT. While HSCT with CCR5Δ32 homozygous donors is not a widely applicable solution for all HIV-1 infected individuals due to its complexity, risks, and the limited availability of suitable donors, it has provided invaluable insights into the potential for achieving HIV-1 remission and a functional cure. Further research is warranted to optimize this strategy, address the challenges of viral rebound, and develop more scalable and accessible cure strategies for a broader population of people living with HIV-1.

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