**International Journal of Pharmaceutical and Bio-Medical Science**

ISSN(print): 2767-827X, ISSN(online): 2767-830X

Volume 01 Issue 02 May 2021

Page No : 21-25

# HIV/Aids Treatment by Stem Cell Transplantation: A Review

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ABSTRACT

Human immunodeficiency virus (HIV) required the presence of CD4 receptor and chemokine receptor (CCR5Δ32) to inter into the CD4 host cell. Antiretroviral drugs only blocks the entry of HIV virus into the host cell. The cure of an HIV/AIDS patient the stem cell transplantation from an allogeneic and autologous donor who are homozygous for CCR5Δ32 receptor mutation has increase research strategies to cure HIV/AIDS to induce long term remission without antiretroviral drugs. Natural CCR5Δ32 deficient donors and autologous stem cell transplantation of genetically modified hematopoietic stem cells are currently under research. This review highlight the previous studies of stem cell transplantation in the treatment of HIV/AIDS.

ARTICLE DETAILS

**Published On:**
**31 May 2021**

**Available on:**
**https://ijpbms.com/**

KEYWORDS: HIV/AIDS, Stem Cell Transplantation

## INTRODUCTION

The infection with human immunodeficiency virus (HIV) leads to lifelong infection to the patient. The human immunodeficiency virus (HIV) is a lentivirus and its causative agent for the AIDS (Acquired immune deficiency syndrome) [1]. The high risk in HIV patient is malignancies and specially for B- non Hodgkin lymphomas. Without highly active antiretroviral therapy (HAART) the patient infected with HIV do not survive. Patient with HIV infection must to be continue lifetime HAART therapy which have so many adverse effect [2][3]. The HIV virus host and replicate into the CD4 T-helper cell into the human body. CCR5Δ32 is the major and important receptor present over the CD4 T-helper cell. Without CCR5Δ32 receptor HIV virus do not able to enter into the CD4 T helper cell which is host cell for the HIV virus replication [4]. The HAART cause toxicity as well as weakness of immune system [5].

Development in the oncology condition treatment like stem cell transplantation, gene therapy is also effective in the HIV as per study. The stem cell is the type of cell which capable to produce specialize type of cell into body. The stem cell have good ability to make number of copies of themselves. In 1980 cell therapy and the Stem cell transplantation give new hope to find the appropriate and effective cure for the HIV [2]. Highly active anti retroviral therapy (HAART) was regularly maintained during the stem cell transplantation in the HIV affected patient. Chemotherapy with blood stem cell transplantation (SCT) is the therapy of choice in relapsed or partially responding HIV lymphoma patients [6][7]. The CCR5Δ32 deficient stem cell help to rebuilding the entire immune system which is possible or likely block the entry of HIV into the CD4 T helper cell [8].

## STEM CELL THERAPY

Stem cell is the type of cell which is capable to produce specialize type of cell into the body [8]. After the discovery of stem cell transplantation it is become the standard treatment in life threatening leukemia, lymphomas as well as some malignant disease like aplastic anemia or thalassemia [9]. There are major concept into the stem cell therapy is Autologous stem cell transplantation and Allogeneic stem cell transplantation. In autologous stem cell transplantation patient donate their own stem cell. In allogeneic stem cell therapy matching donor is required for the stem cell transplantation [10]. Major source for the stem cell in the human body is blood, blood vessel, brain, skin, liver, bone marrow, skeletal muscle [11]. The major criteria for the allogeneic stem cell transplantation is the human leukocyte antigen (HLA) system and 5 gene loci (A, B, C, DRB, DRQ), (Two allelic to each / 10 allelic total) have to be required. Out of Ten-Nine Allelic need to be matched, which is the major issue observed in the autologous transplant patient or stem cell transplantation [12]. The HIV patient also effect on the bone marrow and the myelosuppressive effect of some antiviral drugs. HIV virus able to alter the bone marrow microenvironment and cytokine. But, it does not infect the

primitive stem cells [14]. Antiretroviral therapy also have positive effects on the bone marrow as by improved blood counts in HIV positive patients on HAART without lymphoma [13]. In vivo studies shows increase in marrow mononuclear cells and functional improvement in progenitor cell and stem cell assays with the addition of antiretroviral drugs [14]. But certain antiretroviral drug like Azidothymidine (AZT) are known for myelosuppressive and so, their use is contraindicated in patients previously to stem cell mobilization. Some medical practitioner avoid Azidothymidine in preparation to stem cell collection [7][15]. Age under 18 to 55 with good health are eligible to become stem cell donor. Number of stem cell collected during the stem cell transplantation depends upon the weight of donor, if higher the weight of donor high the number of stem cell. If donor have the problem like life threatening allergies, arthritis, asthma, autoimmune disease, bleeding problem, brain injury, cancer, diabetes, major heart disease, hepatitis, chronic kidney problem, liver disease are not able to donate the stem cell [16].

**Natural HIV resistance stem cell**

The CCR5Δ32 is very important co-receptor present over the CD4 T helper cell which is help to HIV virus entry into host cell [17]. The hematopoietic CCR5Δ32 defective stem cell is serve as a natural HIV resistance cell. There are few people in the world who are naturally resistance to the HIV virus, because their CD4 T helper cell do not have CCR5Δ32 receptor because of some genetic mutation problem. Approximately 10% of the northern European is heterozygous for Δ32 or depletion of CCR5, that is render to protein defective . The beneficial to generating CCR5 is to perform hematopoietic stem cell transplantation using donor who is homozygous for CCR5Δ32 receptor deletion. This approach is limited for patient for donor who is CCR5Δ32 negative [3].

**Stem cell transplantation in treatment of HIV**

The hematopoietic stem cell transplantation (naturally CCR5Δ32 deficient hematopoietic stem cell or artificial CCR5Δ32 deficient stem cell) was done in a patient with HIV infection that was reported some year ago [18]. After the stem cell transplantation the patient did not received antiretroviral therapy and HIV in blood and tissue remained continuously undetectable. This patient known as berlin patient. After this considerable success towards the HIV infection, complete disruption of CCR5 deficient cell is consider as new hopeful approach towards the HIV [19][20]. There are very low availability of the donor who is naturally deficient with CCR5Δ32 receptor over their CD4 T cell. So there are need for alternative method that mimic the natural CCR5 deficiency.

**Method to achieve artificial CCR5Δ32 deficiency on stem cell**

Complete disruption of CCR5 gene, Post transcriptional down regulation of CCR5 gene expression by RNA interference mediated gene silencing, Blocking of CCR5 over the HIV targeted cell [21]. The drug used in ART is just block the cell surface CCR5, it just reduce RNA interference but not eliminate the CCR5 as HIV entry receptor. Other than gene editing change the genetic code of the cell and eliminate the gene function.

**Host genome editing**

There are some very important technologies that help to specific gene changes in the host cell of the HIV.

The technologies are ….

1. Engineered zinc finger nucleases (ZFN)
2. Transcription activator like effector nucleases (TALEN)
3. Clustered regularly interspaced short palindromic repeat (CRISPR).

Now a days ZFN is the most commonly used technology for HIV related gene editing [22]. ZFN is synthetic restriction enzyme that is prepared from targeted zinc finger DNA binding domain and endonucleases domain that allows the sequence selective cleavages of targeted DNA from host cell [23][24]. ZFN technique used to the CCR5 from cell to generate artificial CCR5 deficient cell. Most commonly used cell for preparing CCR5 deficient cell for gene editing are CD4+ T cell and hematopoietic stem cell. ZFN disrupts total 50% of CCR5 alleles in CD4 targeted cell. ZEN treated CCR5 deficient where transplanted in the patient who was suffering from the HIV there is decrease in the level of HIV in the patient [25][26][27]. The TALEN show low toxicity as compare to the ZFN [28]. With the help of engineered ZFNs, scientists try to develop CCR5 gene disruption to look for the cure of HIV/AIDS therapy [27]. The ZFNs identified the CCR5 coding region and generated a double-strand breaks (DSB) at a target site. The permanent disruption of CCR5 gene over the T-cell (host cell for HIV) resulted in interfering HIV infection [29].

TALEN is also an efficient restriction enzyme for achieving gene editing following ZFN, and structurally similar to ZFN.

**Development occurs during the stem cell transplantation in the treatment of HIV in last few years.**

| Year | Development In the stem cell transplantation in the HIV treatment | Reference |
|---|---|---|
| 1981 | Cell transfer without modifying cell | [2] |
| 1984 | Synergetic stem cell transplantation | [30] |
| 1988 | Stem cell transplantation together with anti HIV drug | [31] |
| 1989 | Allogeneic stem cell transplantation | [32] |

| | | |
|---|---|---|
| 1990 | Stem cell transplantation combine with antiretroviral therapy | [33] |
| 2001 | Stem cell transplantation with gene therapy | [34] |
| 2005 | Cord blood us for stem cell transplantation in HIV patient | [35] |
| 2007 | Stem cell transplantation using homozygous cell transplantation | [36] |
| 2010 | Modification in stem cell using ZFN technique | [27] |

**Interaction during stem cell transplantation in the AIDS patient**

It is common thing that the antiretroviral therapy do not stop during the high dose of chemotherapy and in stem cell transplantation. But the patient receive many medication during the period of treatment which may interact with the antiretroviral therapy. For nucleoside reverse transcriptase inhibitor the drug-drug interaction may be negligible, but it have indirect influence on the transporter mediated renal clearance of many other drug [37].

Next problem occur during the anti retroviral therapy and stem cell therapy is the temporary incapability to take the oral medication because the refractory emesis or severe mucositis may cause. This problem may solved with the use of parenteral antiretroviral drugs [38].

Infectious complication may face during stem cell transplantation like BK-virus associated hemorrhagic cystitis, dental infection, Bronchiolitis obliterans with organizing pneumonia, Neutropenic sepsis, etc. [18].

**Immune Recovery in Allogeneic Transplant**

The allogeneic transplantation in HIV positive patients is considerably more scanty than ASCT. Information on allogeneic transplantation in patients with different clutters recommends that the pace of safe reconstitution post-transplant is reliant on elements, for example, the sort of molding routine, HLA similarity of the contributor and have, and the improvement of join versus have illness (GVHD). In a transplant with a HIV negative beneficiary T lymphocyte recuperation happens by thirty days post-transplant, however at first with overwhelmingly CD8+ cells [39]. Recuperation of CD4+ cells can take as long as a half year as does recuperation of ordinary T cell reactions to mitogens. Frequently patients accomplish a condition of halfway chimerism present transplant due on have unite resistance, much the same as that found in strong organ allografting. Patients with non HIV interceded immunodeficiency who accomplish incomplete chimerism with allografting may recoup satisfactory T cell work. It is obscure whether a similar level of recuperation would happen in the HIV contaminated patient [15].

Early reports of allogeneic transplant were within the pre HAART period. Specialists at John's Hopkins wrote about a 40 year old male with HIV lymphoma who got TBI cyclophosphamde molding followed by allogeneic bone marrow mixture. Pre transplant he got high portion AZT and post-transplant he got a lower portion [32]. There was no critical routine related harmfulness. The patient engrafted at day +17 in any case passed on of lymphoma at day +47. At examination, no proof of HIV either by culture or PCR was found in tissue examples. This early experience underscored the plausibility of the strategy. All the previously mentioned investigations affirmed the plausibility, decency and adequacy of high portion treatment and ASCT in HIV patients. In vitro investigations of safe reconstitution, for example, interleukin 7 levels, T cell subsets and T cell V-Beta collections in few HIV patients who experienced ASCT affirm the strength of safe reconstitution [40].

**The berlin patient**

The first report of the HIV infected patient who cured from the HIV infection with hematopoietic stem cell transplantation (HSCT) gave extreme hope and curiosity in the HIV treatment. In 2007 the patient had HIV infection as well as leukemia was transplanted in berlin using hematopoietic stem cell (HSC) from donor whose cell don't have CCR5 receptor which is essential for HIV to inter into the host cell [3]. After stem cell transplantation the anti-retroviral therapy was stopped and after some period of time the HIV was undetectable [20]. After transplantation with donor who deficient for CCR5 HIV resistance stem cell, it totally reconstitute his immune system, giving the hope that HIV may cured.[41][42]

**Success of stem cell transplantation in HIV/AIDS cure**

In year 2007, timothy ray brown become the first person whom doctor announced to be cured from HIV. We referred him as berlin patient. Mr. Brown received antiretroviral therapy for HIV in year 1990. After receiving stem cell transplantation he not only cured with leukemia as well as from HIV/AIDS infection [43][44].

In second case Adam Castillejo from london, the patient who had both HIV/AIDS and Hodgkin lymphoma received stem cell transplantation with the cell which do not have CCR5 gene. After 30 months the patient stopped antiviral therapy, doctor confirmed that the HIV count in the blood sample was undetectable.

**CONCLUSION**

The role of stem cell transplantation is good in treatment of HIV/AIDS. Several studies shows that stem cell transplantation in the patient with HIV infection treatment is possible and it has low regimen related toxicity (RRT). It is clear that stem cell transplantation could contribute in the treatment of HIV/AIDS in so many ways. The ZFN, TALEN, CRISPER is very most important method to disrupt the

CCR5Δ32 receptor from the CD4 cell if the natural CCR5Δ32 receptor stem cell is not available. However the first cases with HIV/AIDS cures with the help of stem cell transplantation treatment give the hope that this unique case will not stand alone in the future.

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