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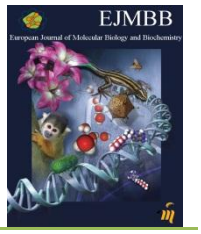

STEM CELL TRANSPLANTATION IN HIV PATIENTS: AN EXCITING PROMISE FOR CURE?

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ABSTRACT
Survival of patients with HIV infection has improved considerably since the introduction of highly active antiretroviral therapy (HAART) but current approaches in HIV Therapy do have limitations. HIV DNA persists as 'integrated genome', so such ARVs (anti-retro virals) are unlikely to prove 'curative'. These therapies require long term 'adherence' to remain effective, associated with long term toxicities, chronic inflammation, T-cell dysfunction, and are expensive & hard to be delivered on world basis since then. Naturally people have started conjecturing for some kind of cure /eradication. Stem-cell transplantation from an HLA-matched donor (allo SCT) has failed in previous times, but one report a 40-year-old man, with HIV-1 infection since 1995 having a relapse of acute myeloid leukemia (AML) first diagnosed in 2006,.who underwent allogeneic stem cell transplant (allo SCT) with a donor selected to be homozygous for CCR5-δ32.and remaining free from the disease ever, has generated considerable amount of excitement and hope among people for for PLHAs (people living with HIV/AIDS) , for some kind of cure, even in form of 'a functional 'one.

INTRODUCTION

The scientific literature, and relevant political headlines were surveyed which illuminated the stem cell role in treatment for HIV and were summarized for this review. Building on this conceptual frame work, the related issues of clinical promise enveloping this emerging technology were examined. An interesting *case report pointing to gene therapy as a potential avenue for controlling HIV without antiretroviral therapy, by stem cell transplantation* (called 'Berlin Patient' 2nd) has been reported in, *Med Univ of Berlin, Germany, and New England Journal of Medicine*, which begun with a request at the Bone Marrow Donor Registry revealing 232 HLA-identical donors for this patient. Donors were screened for

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the deletion using a genomic polymerase chain reaction (PCR) assay. The patient received peripheral stem cells from donor #61, identified to be homozygous for CCR5-δ32. HAART was stopped from day of transplantation. To determine co-receptor usage of the patients` HIV-1 phenotype, the V3 region of the HIV-1 *env* gene was amplified. The susceptibility of peripheral blood mononuclear cells (PBMC) towards infection was determined by limiting dilution experiments using defined HIV-1 strains. Quantification of HIV-1 infection was measured by measurement of HIV-1 RNA and proviral cDNA using the *env* and long terminal repeat (LTR) region in peripheral blood, bone marrow, and rectal mucosa [1-3].

RESULTS

During the whole follow-up period, measurement of serum HIV-1-RNA remained negative and the semi-quantitative proviral DNA assay was under the limit of detection since day +61.

DISCUSSION

Destruction of the immune system by the human immunodeficiency virus (HIV) is driven by the loss of CD4+ T cells in the peripheral blood and lymphoid tissues. Viral entry into CD4+ cells is mediated by the interaction with a cellular chemokine receptor, the most common are CCR5 and CXCR4. Since subsequent viral replication requires cellular gene expression processes, activated CD4+ cells are the primary targets of productive HIV infection. Consequently, HIV infection leads predominantly to the depletion of activated memory CD4+ T cells, the vast majority of which reside in the gastrointestinal (GI) mucosa Although therapeutical control of HIV replication allows the immune system to partially restore and delays disease progression, cure of HIV infection remains still unachievable with the currently available antiretroviral drugs. The major barrier to viral eradication in patients receiving antiretroviral therapy (ART) is the establishment of HIV reservoirs including low- level productively and latently infected cells. Thus, maintenance of replication-competent HIV in long-lived cells and distinct anatomical sanctuaries allows the virus to reseed the body once ART is discontinued Cells of individuals homozygous for the CCR5 gene variant Δ32 (CCR5Δ32/Δ32) are naturally resistant to infection with CCR5-tropic HIV strains (R5 HIV) due to the lack of CCR5 cell surface expression Previously, we demonstrated the feasibility of hematopoietic stem cell transplantation with CCR5Δ32/Δ32 donor cells (CCR5Δ32/Δ32 SCT) in an HIV- infected patient with relapsed acute myeloid leukemia (AML) and documented absent viremia during the first 20 months of remission while the patient did not receive ART.This case clearly emphasizes the importance for continuing research in the field of CCR5 targeted treatment strategies, but uncertainty remained over whether cure of HIV infection has been achieved in this patient. In the setting of HIV infection, the effects of pre-transplant conditioning do not allow the complete elimination of HIV, as demonstrated by previous studies showing that HIV-infected patients with a stem cell transplant generally experience viral rebound when ART is discontinued. For this reason, together with the fact that CXCR4-tropic HIV variants (X4 HIV) were present within the patient's pre-transplant HIV population, it was reasonable to hypothesize that HIV from the viral reservoir may reseed the body once the immune system has efficiently been restored with X4 HIV susceptible target cells.

Doctors who carried out a stem cell transplant on an HIV-infected man with leukaemia in 2007 say they now believe the man to have been cured of HIV infection as a result of the treatment, which introduced stem cells which happened to be resistant to HIV infection [4].

The man received bone marrow from a donor who had natural resistance to HIV infection; this was due to a genetic profile which led to the CCR5 co-receptor being absent from his cells. The most common variety of HIV uses CCR5 as its 'docking station', attaching to it in order to enter and infect CD4 cells, and people with this mutation are almost completely protected against infection.

The case was first reported at the 2008 Conference on Retroviruses and Opportunistic Infections in Boston, and Berlin doctors subsequently published a detailed case history in the *New England Journal of Medicine* in February 2009.They have now published a follow-up report in the journal *Blood*, arguing that based on the results of extensive tests, It is reasonable to conclude that cure of HIV infection has been achieved in this patient." This man better phased as 'Berlin patient' 2 ,is an HIV-positive man who developed acute myeloid leukaemia, received successful treatment and subsequently experienced a relapse in 2007 that required a transplant of stem cells.

Doctors chose stem cells from an individual who had an unusual genetic profile: a mutation inherited from both parents that resulted in CD4 cells that lacked the CCR5 receptor. This mutation, called CCR5 delta 32 homozygosity, is present in less than 1% of Caucasians in northern and Western Europe, and is associated with a reduced risk of becoming infected with HIV.

This is because all new infecting viruses need to use the CCR5 receptor on CD4 cells when infecting an immune system cell of the CD4 type. Later in the course of HIV infection another type of virus emerges that can use the CXCR4 receptor instead [5].

Before the stem cell transplant the patient received chemotherapy treatment that destroyed most immune cells and total body irradiation, and also received immunosuppressive drugs to prevent rejection of the stem cells. Antiretroviral therapy was halted on the day of the transplant, and the patient had to receive a second stem cell transplant 13 days after the first one, due to a further relapse of leukaemia.

The patient continued to receive immune suppressive treatment to prevent rejection for 38 months,

and at 5, 24 and 29 months post-transplant colon biopsies were taken to investigate possible graft-versus-host disease in the intestine. At each investigation additional samples were taken to check for signs of HIV infection in the abundant immune cells of the gut wall. During the 38 month follow-up period the donor CD4 cells repopulated the mucosal immune system of the gut, to such an extent that the frequency of CD4 cells was almost twice as high as in HIV-negative healthy controls, and this phenomenon was also seen in a control group of ten HIV-negative individuals who received stem cell transfers. The repopulation of CD4 cells was accompanied by the complete disappearance of host CD4 cells, and after two years the patient had the CD4 count of a healthy adult of the same age [6].

One of the challenges for any approach to curing HIV infection is long-lived immune system cells, which need to be cleared before a patient can be cured. In the case of the Berlin patient CCR5-bearing macrophages could not be detected after 38 months, suggesting that chemotherapy had destroyed these longer-lived cells, and that they had also been replaced by donor cells.

The patient did not resume antiretroviral therapy after the transplant. Nevertheless HIV remained undetectable by both viral load testing (RNA) and tests for viral DNA within cells, and HIV antibody levels declined to the point that the patient has no antibody reactivity to HIV core antibodies, and only very low levels of antibodies to the HIV envelope proteins.

Seventeen months after the transplant the patient developed a neurological condition, which required a brain biopsy and lumbar puncture to sample the cerebrospinal fluid for diagnostic purposes. HIV was also undetectable in the brain and the CSF. An additional indication that HIV is not present lies in the fact that the patient's CD4 cells are vulnerable to infection with virus that targets the CXCR4 receptor. If any virus with this preference was still present, the researchers argue, it would be able to swiftly infect the large population of memory CD4 cells that has emerged.

The Berlin patient is a phrase that has been used on two distinct and unrelated occasions to describe a person who has received a functional cure for HIV/AIDS in Berlin, Germany. The first Berlin patient was described in 1998. After receiving an experimental therapy (didanosine, indinavir and hydroxyurea), the patient, who has remained anonymous, has maintained low levels of HIV and has remained off antiretroviral therapy. The world-renowned "second" Berlin patient, *Timothy Ray Brown* which we are talking over here who received a stem cell transplant from a donor naturally resistant to HIV and has remained off antiretroviral therapy since the first day of his stem cell transplant.

Their stories were chronicled in the 2014 book, *Cured: The People who Defeated HIV*.

On similar account the Visconti Cohort, a group of fourteen patients who received early therapy for the virus, are considered functionally cured of HIV, meaning that they still harbor the virus within their bodies but do not need to take antiretroviral therapy. A child known as the Mississippi baby was once considered part of this elite group but has since suffered a relapse. Timothy Ray Brown is the only individual who is considered to have a sterilizing cure, meaning he no longer harbors the HIV virus within his body [7].

Timothy Ray Brown is originally from Seattle, Washington. US He was diagnosed with HIV in 1995 and began antiretroviral therapy. In 2006, Timothy was diagnosed with acute myeloid leukemia (AML). His physician, Dr. Gero Hütter, at Charité Hospital in Berlin, arranged for him to receive a hematopoietic stem cell transplant from a donor with the "delta 32" mutation on the CCR5 Receptor This mutation, found at relatively high frequencies in Northern Europeans (16%), results in a mutated CCR5 protein The majority of HIV cannot enter a human cell without a functional CCR5 gene. An exception to this is a small minority of viruses that use alternate receptors, suchas CXCR4 or CCR2.[12] Those individuals who are homozygous for the CCR5 mutation are resistant to HIV and rarely progress to AIDS. Timothy received two stem cell transplants from one donor homozygous for the delta32 mutation: one in 2007 and one in 2008. Timothy stopped taking his antretroviral medication on the day of his first transplant. Three months after the first stem cell transplant, levels of HIV rapidly plummeted to undetectable levels while his CD4 T cell count increased. In addition, blood and tissue samples from areas of the body where HIV is known to hide were tested. The results were published in the *New England Journal of Medicine*.

Today, Timothy still remains off antiretroviral therapy and is considered cured though some debate exists whether there is no trace of the virus in his body (a "sterilizing" cure) or whether he simply no longer needs treatment (a "functional" cure). In 2012, Timothy Ray Brown announced the formation of an organization whose sole purpose is to find a cure for AIDS called the Cure for AIDS Coalition. The first project of the Cure for AIDS Coalition is the Cure Report launched on October 16, 2014 during the NIH Strategies for an HIV Cure meeting held in the Washington, DC area [8].

CONCLUSIONS

It was demonstratable that the first successful performance of an allogeneic stem cell transplantation in an HIV^+ patient with a donor selected to be homozygous for the CCR5-δ32-allele. Although HAART is discontinued since more than 3years, HIV-1-load could not be detected in peripheral blood, bone marrow, and rectal mucosa. This finding has provided a possible therapeutic option for HIV-infected patients.

Implications

If a cure has been achieved in this patient, it points the way towards attempts to develop a cure for HIV infection through genetically engineered stem cells.

The findings point to the importance of suppressing the production of CCR5-bearing cells, either through transplants or gene therapy.

Scientists were sufficiently intrigued by the Berlin patient that they met in Berlin in 2009 to discuss how they could coordinate efforts to identify CCR5-delta32 homozygous donors and expand the supply of stem cells from these donors, for example through sampling blood cells from the umbilical cord of babies born to mothers who are homozygous for CCR5-delta32, in order to eventually facilitate stem-cell therapy.

Gene therapy techniques which can transform stem cells – and all their descendents – into cells resistant to HIV entry may be a more practical option than looking for matching donors [9].

Several US research groups announced in October 2009 that they had received funding to explore techniques for engineering and introducing CCR5-deficient stem cells.

If these approaches prove successful they will be expensive, so in the early stages it is likely that they would be reserved for people with no remaining treatment options or a cancer requiring bone marrow or stem cell transfer.

As Timothy Brown's experience shows, curing HIV infection through ablative chemotherapy, immunosuppressive drugs and stem cell transfer is not a course of treatment for the faint-hearted. It has required courage, determination and a lot of support to become the first person to be pronounced `cured` of HIV infection.

A cure for HIV has always been the holy grail of HIV research though 'Cure' do have philosophical, and programmatic connotations in the context of HIV /AIDS. Many developments and strategies have been evolved to tame this virus, since it's reporting - some 32 years ago. Medical fraternity is reacting with guarded appreciation and anticipation, more so after the publication of reports of Sterilizing /functional cure of a man (this Berlin patient') following BMT from a donor having deficient chemo co receptor CCR5 so vital for HIV entry and one baby, known as 'Mississippi Baby' who was infected with HIV at birth but was apparently free of the virus. For some period through a hit hard, hit early approach taken by researchers and doctors in relation to antiretroviral therapy These findings hold out the hope that treatment during acute HIV infection (ala–Mississippi baby) has the potential to transform the outcome of HIV infection in at least some individuals The use of early and aggressive treatment could be a paradigm shift in HIV/AIDS treatment in children in the developing world, where mothers are typically treated during pregnancy to lower the risk of passing the virus on to the child. Both long-term survivors and those who have been exposed to HIV but remain sero negative (called Elite Controllers and Slow/Non Progressors) offer a great opportunity to study the mechanisms of resistance to HIV infection and disease. Till 'Cure' is not achieved we will have to remain steadfast in working towards it.

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