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The Additional Use of Viral Entry Inhibitors during Autologous Hematopoietic Stem Cell Transplantation in Patients with Non-Hodgkin Lymphoma and HIV-1 Infection

The survival of patients infected with human immunodeficiency virus type 1 (HIV-1) has considerably improved since the introduction of antiretroviral therapy (ART). However, therapy is associated with serious problems, including toxic side effects, and the mortality rate is high among HIV-1-infected patients who are unable to receive ART or have developed late-stage acquired immunodeficiency syndrome (AIDS) [1]. ART prevents de novo infection of target cells, and theoretically, once full suppression of HIV-1 replication is achieved, viral eradication will occur when all preexisting cellular reservoirs decay to the point that no virus is present [2]. In practice, it has not been possible to eradicate HIV-1 in patients, mainly because of the persistence of latently infected $CD4^+$ T cells, especially in gut-associated lymphoid tissues [3]. These rare cells represent only 1 per million $CD4^+$ T cells, but their decay rate is very slow. It has been suggested that latently infected $CD4^+$ T cells have a half-life of about 44 months. HIV-1 eradication would thus take over 60 years of continuous suppressive ART (Figure 1A) [4].

CCR5 IN MAINTAINING HIV-1 INFECTION

CC chemokine receptor 5 (CCR5) and CXC chemokine receptor 4 (CXCR4) have been identified as 2 major coreceptors for entry of HIV-1 into host cells. A 32-basepair deletion in the CCR5 allele (CCR5-delta32) leads to a truncated gene product and provides resistance against HIV-1 transmission in individuals homozygous for this mutation. The decisive role of CCR5 in maintaining HIV infection was substantiated by the first allogeneic stem cell transplantation (SCT) in an HIV-1-infected patient from a donor homozygous for the CCR5-delta32 deletion [5]. Transplantation led to a change in the patient's CCR5 allele genotype. Finally, HIV remains undetectable for more than 2 years after discontinuing ART, as determined by viral RNA and proviral DNA PCR assays of peripheral blood (PB), bone marrow (BM), cerebral fluid, and gut mucosa.

Possible explanations for this finding are: (1) The conditioning regimen for SCT led to depletion of the T cell pool and thus significantly reduced the HIV-1 reservoir. (2) Under immunosuppressive treatment, the absence of activated $CD4^+$ T cells abrogated HIV-1 replication in the remaining T cell fraction. (3) Repopulating $CD4^+$ T cells were resistant to CCR5-tropic HIV-1 infection because of the absence of CCR5 surface expression. (4) Reconstitution of the T cell pool was too slow to provide an adequate number of $CD4^+$ target cells for the reemergence of HIV-1 infection via coreceptors other than CCR5.

IMPROVING ELIMINATION OF LATENTLY INFECTED CELLS

Patients with HIV infection have a much higher risk of developing non-Hodgkin lymphoma than the general population, and it has been suggested that there will be a rising demand for intensified antitumor treatment options like SCT [6]. Two prerequisites must be met to translate our finding of viral control after allogeneic SCT into a more feasible and practicable approach: (1) reduction of HIV-1 infected cells by T cell depletion, and (2) interference with at least 1 of the coreceptors on repopulating cells by either pharmacologic or genetic means. The first prerequisite is met in patients receiving high-dose chemotherapy with profound but reversible T cell depletion to treat malignancies. To fulfill the second prerequisite, entry inhibitors targeting CCR5 and/or CXCR4 should administered in addition to conventional ART during conditioning regimen in patients receiving SCT, at least until T cell recovery is completed. Clinical experience with CCR5 inhibitors has been gained in the MOTIVATE 1 and 2 trials, where participants receiving maraviroc achieved a significant reduction of the viral load compared to those taking placebo [7]. Gene therapeutic knock down of HIV entry coreceptors by modification of hematopoietic stem cells (HSCs) could provide an effective alternative. In a nonhuman primate model, the transduction of anti-CCR5 siRNA into HSCls led to a stable reduction of CCR5 over a period of 14 months [8].

In summary, HIV-1 therapy that interferes with the entry mechanism seems to be a promising approach and is still being developed. The procedure just described may significantly reduce the HIV reservoir to slow disease progression or shorten the estimated time required for viral eradication (Figure 1B).

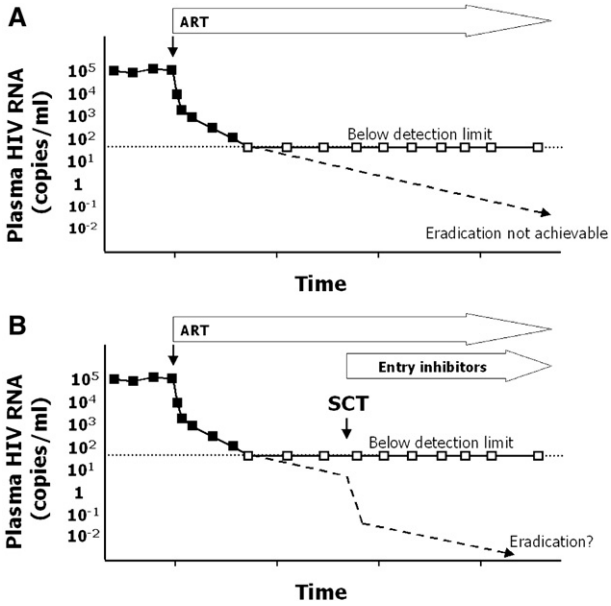

Figure 1. Course of HIV-1 infection. **(**A) Course of viral load in HIV-1 infection after initiating antiretroviral therapy (ART). After a primary rapid decline, the decrease in HIV-1 load stagnates because of the long half-times of latently infected T cells. When HIV-1 RNA levels drop below the detection limit, the viral load dynamics cannot be adequately predicted. Mathematical algorithms for predicting T cell half-times indicate that HIV-1 eradication cannot be achieved in the course of a lifetime. (B) T cell depletion, for example during SCT, with additional administration of HIV-1 entry inhibitors may reduce the number of latently infected T cells, protect against reinfection, and thus reduce the time to viral eradication by antiretroviral therapy. [Modified from Sedaghat et al. *PloS Pathog.* 2007.]

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