RESULTS. Before HSCT, the patient’s virus was shown to use the CCR5 coreceptor. The patient required 2 transplants because of acute myeloid leukemia relapse. However, the patient’s antiretroviral therapy was stopped before the first transplant and was not restarted. After the second transplant, 100% chimerism of the patient’s peripheral blood was demonstrated. Strikingly, the patient’s viral load in plasma and lymphocytes remained undetectable for 20 months after HSCT and discontinuation of antiretroviral therapy.

CONCLUSIONS. This report provides “proof of concept” that HIV may be controlled (or eliminated) after HSCT with cells intrinsically resistant to HIV infection.

REVIEWER COMMENTS. The accompanying commentary (Levy JA. N Engl J Med. 2009;360[7]:724–725), titled “Not an HIV Cure, But Encouraging New Directions,” perhaps understates what happened for this single patient; it is indeed possible that he was cured of his HIV. Although this is not applicable to the vast majority of HIV-infected individuals, this approach can be adapted for more-general use. For example, ongoing studies are being performed with autologous hematopoietic stem cells that have been genetically manipulated to mimic the unfavorable conditions for the virus that occur naturally in homozygous CCR5 Δ32 individuals. Insertion of genes that downregulate CCR5 expression, interfere with HIV replication, or both is an area of intense investigation. Although the initial costs of such an approach are substantial, the long-term costs of antiretroviral drugs and other interventions likely would make this approach, if it works, cost-effective.

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Long-term Control of HIV by CCR5 Delta32/Delta32 Stem-Cell Transplantation


PURPOSE OF THE STUDY. HIV infection of a target cell requires the expression of CD4 and a chemokine receptor. Early after HIV transmission, the chemokine coreceptor used most often is chemokine receptor 5 (CCR5). Approximately 1% of Northern European individuals possess homozygosity for a 32-base pair deletion (Δ32) in their CCR5 genes. These individuals are exceptionally resistant to HIV infection with CCR5-expressing HIV. The purpose of this study was to determine whether HIV could be suppressed by hematopoietic stem cell transplantation (HSCT) from a donor homozygous for CCR5 Δ32.

STUDY POPULATION. One HIV-infected adult was studied.

METHODS. The patient had been diagnosed with HIV ~10 years before the development of acute myeloid leukemia. He had been treated effectively with antiretroviral agents and, at the time of the leukemia, his CD4+ T-cell count was 415 cells per mm³ and HIV RNA was undetectable. The leukemia was initially treated with chemotherapy but relapsed. The patient underwent allogeneic HSCT. The donor was chosen from a long list of potential donors who were HLA identical to the patient. The specific donor was chosen because of his homozygosity for the CCR5 Δ32 mutation.

RESULTS. Seventy-eight percent of subjects receiving raltegravir achieved complete viral suppression. In that year, given the drugs that were available at the time, treatment of HIV with single agents does not result in suppression to <50 copies per mL at 48 weeks was achieved by 62% of raltegravir-treated subjects, compared with 33% of placebo recipients. Raltegravir was very well tolerated. The most common drug-related adverse events were increased serum cholesterol, triglyceride, and amino-transferase levels in the raltegravir group and increased cholesterol and creatinine levels and decreased neutrophil counts in the placebo group. Clinical adverse events were similar between groups, and rates of discontinuation because of drug-related events were also similar in the raltegravir and placebo groups.

CONCLUSIONS. In heavily pretreated, HIV-infected patients with limited treatment options, raltegravir plus optimized background therapy provided better viral suppression than did optimized background therapy alone for ≥48 weeks.

REVIEWER COMMENTS. Since 1995, it has been apparent that treatment of HIV with single agents does not result in complete viral suppression. In that year, given the drugs that were available at the time, ≥3 antiretroviral agents were required to suppress HIV RNA levels to <50 copies per mL. It is clear from the raltegravir and maraviroc studies that the addition of a single active agent, regardless of potency or mechanism of action, is not sufficient to achieve this end. However, given the new agents now available, patients with multidrug-resistant HIV have excellent chances of achieving viral suppression, often with 2 active agents. The availability of potent new agents active against multidrug-resistant HIV is welcome news to clinicians and patients still facing the daunting task of maintaining control over a remarkably resilient microbe.

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