retroviral agents. The purpose of this study was to evaluate a CCR5 antagonist, maraviroc, in the treatment of HIV-infected adults.

STUDY POPULATION. Two double-blind, placebo-controlled studies were conducted. More than 1000 patients were randomly assigned to receive either maraviroc or placebo in combination with investigator-chosen optimized background therapy. Most patients were resistant to multiple classes of antiretroviral agents; mean baseline viral loads were >72,000 copies per mL, and median CD4+ cell counts were 169 cells per mm3.

METHODS. Subjects were assigned to receive maraviroc or placebo in addition to optimized background therapy based on treatment history and drug resistance testing. Safety and efficacy were assessed after 48 weeks.

RESULTS. The demographic and baseline characteristics of patients were similar between the 2 study groups (placebo and active drug). A significantly greater proportion of individuals receiving placebo discontinued treatment, primarily because of lack of efficacy. The primary end point of the study, mean change in plasma levels of HIV RNA, was substantially greater for maraviroc-treated patients than placebo-treated patients (−1.82 log10 copies per mL in the maraviroc-treated group, compared with −1.079 log10 copies per mL in the placebo-treated group). Secondary end points included the proportion of subjects who achieved undetectable viral loads (<50 copies per mL of plasma) at 48 weeks. Forty-seven percent of individuals receiving maraviroc twice daily achieved viral suppression, compared with ~18% of placebo-treated patients. Finally, the improvement in circulating CD4+ T-cell counts was substantially greater in the maraviroc-treated patients (~122 cells per mm3 gained), compared with the placebo-treated subjects (69 cells per mm3 gained). Maraviroc was well tolerated. Rates of discontinuation because of adverse events related to study treatment were the same in the placebo and maraviroc groups. Rates of serious adverse events were similar among the treatment groups (~18%–20%), and rates of laboratory abnormalities were similar among the study groups.

CONCLUSIONS. Maraviroc was well tolerated, and adverse events were no greater than in the placebo group. Maraviroc treatment resulted in greater suppression of HIV, greater increases in CD4+ cell counts, and a greater proportion of individuals who achieved HIV RNA levels of <50 copies per mL.

REVIEWER COMMENTS. This study and its companion article (Fäktenerhue G, Nelson M, Lazzarin A, et al. N Engl J Med. 2008;359[14]:1442–1455) demonstrated that maraviroc is an effective antiretroviral agent. It achieved remarkable success in a very heavily pretreated population. Of particular importance was the need for at least 1 and preferably 2 effective agents in the optimized background regimen to maximize the effect of maraviroc. In addition, in the secondary analysis of the results, pre-existing CXCR4-using HIV essentially eliminated any benefit of maraviroc. The development of CXCR4-using HIV after primary infection with CCR5-using virus is a matter of time and chance. Approximately 50% of heavily pretreated, long-term HIV-infected adults have CXCR4-using virus and thus would be completely resistant to maraviroc therapy. Currently, maraviroc is approved for patients who are known to be resistant to multiple other drugs. Perhaps maraviroc and similar chemokine receptor blockers would best be used before the likely development of CXCR4-using virus. Studies are underway to evaluate the use of this novel agent in patients naive to antiretroviral therapy.

Joseph A. Church, MD
Los Angeles, CA

Raltegravir With Optimized Background Therapy for Resistant HIV-1 Infection

PURPOSE OF THE STUDY. As described above, there are compelling reasons for expanding the anti-HIV armamentarium. Raltegravir is an inhibitor of HIV integrase, an enzyme essential in the cycle of HIV replication. Because it belongs to a novel class of antiretroviral agents, the drug should be effective against HIV that is resistant to other antiretroviral drugs. The purpose of this study was to evaluate the safety and effectiveness of raltegravir in adults with multidrug-resistant virus.

STUDY POPULATION. HIV-infected patients ≥16 years of age were eligible if they had plasma HIV RNA levels of >1000 copies per mL and documented resistance to ≥1 drug in each of the 3 classes of antiretroviral drugs (ie, nucleoside transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and protease inhibitors).

METHODS. Two identical trials in different geographic regions were conducted to evaluate raltegravir versus placebo in combination with optimized background anti-HIV therapy. Patients were randomly assigned to receive raltegravir or placebo, in a 2:1 ratio. Clinical status was assessed regularly during the trial, and protocol-mandated laboratory studies were performed at a central laboratory. The primary end point of the study was the proportion of patients achieving HIV RNA levels of <400 copies per mL after 16 weeks of study therapy.

RESULTS. Subjects (N = 699) were enrolled in studies in the different geographic locations. Because results were very consistent between the 2 substudies, combined re-
results are presented. Subjects receiving raltegravir were well matched to the subjects receiving placebo. Seventy-eight percent of subjects receiving raltegravir achieved the primary end point of <400 copies of HIV RNA per mL, compared with ~42% for those receiving placebo. This difference persisted through week 48 of the study (72% vs 37%). HIV RNA 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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Joseph A. Church, MD
Los Angeles, CA

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. 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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Joseph A. Church, MD
Los Angeles, CA
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Joseph A. Church

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