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Xenotransplantation of Hematopoietic Cells Resistant to HIV as a Potential Treatment for Patients With AIDS

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OF THE two types of retroviruses that have been isolated in patients with acquired immunodeficiency syndrome (AIDS), human immunodeficiency virus-1 (HIV-1) is the more common in the United States, Europe, and Central Africa. Very few monkeys have been successfully infected with HIV-1, including chimpanzee and gibbon apes. Some of the inoculated animals have developed high titer virus-specific antibody responses after infection. However, no animal has developed the disease.[1] Generally, small animal species, such as rodents, are even more resistant to AIDS and are not susceptible to HIV infection through normal routes.[2] The spread of AIDS and HIV infection has become a global concern and the search for a cure has been hampered by the lack of suitable animal models.

We propose to consider these "negative results" in the development of suitable animal models as a potential clue for the treatment, that is, to verify whether hematopoietic cells from a donor that does not develop AIDS can transfer disease resistance to an infected recipient. If patients with AIDS could be successfully transplanted with xenogeneic bone marrow cells (BMC) from a resistant species, a gradual replacement of the dying lymphoid cells of the recipient could occur, with BMC from the resistant donor that could selectively survive.[3] We report the first attempt to verify this hypothesis by reconstitution of an AIDS patient with xenogeneic bone marrow from a resistant species, the baboon.

PATIENT AND METHODS

The recipient was an HIV-positive, 56-year-old male with advanced AIDS (pancytopenia, malnutrition, dehydration, metabolic acidosis, chronic *Cryptosporidium* diarrhea). Lymphocytotoxicity cross-match was strongly positive (titer 1:2; DTT negative). Cross-matching of patient serum against baboon red blood cells (RBCs) indicated a human antibaboon heteroagglutinin titer of 1:4 (room temperature) and 1:32 (Coombs phase). The donor bone marrow was depleted of RBCs resulting in a loss of BMC from 30×10^9 before, to 6.6×10^9 after depletion. The final dose of BMC infused was 0.94×10^8/kg BMC, comprising 0.48×10^6/kg $CD4^+$ cells. Immunosuppression was with FK-506, Cytoxan, PGE-1, and steroids. Primers recognizing the chorionic gonadotropin gene of the baboon were used for amplification followed by Southern blot to detect baboon DNA in the recipient at different times after transplantation. HIV titer was measured by quantitative microcultures performed following serial dilutions PBMC that were co-cultured with 1×10^6 stimulated normal PBMC. Following culture for 21 days, virus production was measured by p24 assay in culture supernatants.

RESULTS AND DISCUSSION

Xenogeneic BMC infusion was well tolerated by the patient and did not produce any early complication such as anaphylaxis or graft-versus-host disease. However, no significant change was observed in circulating CD4 levels, CD4/CD8 ratio, and cell-associated HIV titer during the follow-up (Table 1). Polymerase chain reaction (PCR) results were negative for baboon DNA at 3 to 47 days. The patient was discharged 53 days posttransplant and eventually died 2 weeks later of progressive disease. The results indicated that the baboon BMC failed to engraft. However, xenogeneic BMC infusion did not produce early complications. Without evidence for xenogeneic BMC engraftment, it was not possible to determine the potential of this approach to treat AIDS. We have recent evidence that chimerism can be obtained by BMC xenotransplantation across these species. Two baboons that were treated with a single dose of total lymphoid irradiation (TLI, 750 Gy) before receiving a human bone marrow infusion, were positive for human DNA (PCR) over 6 months following xenotransplantation. The animals did not receive any additional immunosuppressive treatment following the single dose of TLI (P. Fontes et al, manuscript in preparation). In addition, we have recently infused baboon bone marrow in a patient who received a liver transplant from the same donor.[5] In this case, the baboon bone marrow was not treated to remove RBCs and baboon DNA was detected during the follow-up, indicating that a state of

Table 1.

	Pretransplant	Day 7	Day 15	Day 28
WBC count	3.5	3.6	6.4	5.9
Lymph	210	72	256	177
CD4(%)	2(1)	4(5)	15(6)	TFTC
CD4/CD8	0.03	0.06	0.1	TFTC
HIV titer	4	256	<1	1

Abbreviations: WBC, white blood cell; HIV, human immunodeficiency virus; TFTC, too few to count.

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microchimerism was established. However, it cannot be excluded that the donor liver was responsible for the recipient chimeric state, because it is now known that chimerism is present in recipients of any organ transplant.[4] Further studies are needed to determine the ideal donor species that could be used for hematopoietic reconstitution of patients with AIDS, and the ideal induction and/or immunosuppressive treatment to establish a chimeric state in the recipients.

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