CRISPR-Edited Stem Cells in a Patient with HIV and Acute Lymphocytic Leukemia

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SUMMARY

The safety of CRISPR (clustered regularly interspaced short palindromic repeats)–based genome editing in the context of human gene therapy is largely unknown. CCR5 is a reasonable but not absolutely protective target for a cure of human immunodeficiency virus type 1 (HIV-1) infection, because CCR5-null blood cells are largely resistant to HIV-1 entry. We transplanted CRISPR-edited CCR5-ablated hematopoietic stem and progenitor cells (HSPCs) into a patient with HIV-1 infection and acute lymphoblastic leukemia. The acute lymphoblastic leukemia was in complete remission with full donor chimerism, and donor cells carrying the ablated CCR5 persisted for more than 19 months without gene editing–related adverse events. The percentage of CD4+ cells with CCR5 ablation increased by a small degree during a period of antiretroviral-therapy interruption. Although we achieved successful transplantation and long-term engraftment of CRISPR-edited HSPCs, the percentage of CCR5 disruption in lymphocytes was only approximately 5%, which indicates the need for further research into this approach. (Fundied by the Beijing Municipal Science and Technology Commission and others; ClinicalTrials.gov number, NCT03164135.)
CCR5 disruption in human HSPCs with an efficiency of 27%. In an animal model, these CCR5-modified HSPCs robustly generated a human immune system that was resistant to HIV-1 infection. Here, we report the allogeneic transplantation of CCR5-edited HSPCs into a patient with HIV-1 infection in whom acute lymphoblastic leukemia had developed.

CASE REPORT

A 27-year-old man received diagnoses of HIV–AIDS (acquired immunodeficiency syndrome) and acute lymphoblastic leukemia (T-cell type) on May 14 and May 30, 2016, respectively. At diagnosis, the HIV viral load was $8.5 \times 10^6$ copies per milliliter, and the CD4+ cell count was $528 \times 10^6$ per liter. Antiretroviral drugs (lamivudine at a dose of 300 mg daily, tenofovir at a dose of 300 mg daily, and lopinavir–ritonavir at a dose of 400 mg of lopinavir and 100 mg of ritonavir twice daily) were immediately administered, which resulted in control of HIV-1 infection and undetectable virus RNA in the serum (<40 copies per milliliter) after 1 year. The patient received six courses of standard chemotherapy for acute lymphoblastic leukemia (see the Methods: Chemotherapeutic Regimens section in the Supplementary Appendix, available with the full text of this article at NEJM.org), which led to morphologic complete remission. The minimal residual disease, determined by means of flow cytometry, was 3.10% and 0.04% before the fifth and sixth courses of chemotherapy, respectively, and became undetectable (<0.01%) after the sixth course.

The infecting HIV was determined to be CCR5-tropic on the basis of previously described methods. The patient had an undetectable plasma HIV RNA level and had lymphopenia (CD4+ cell count, $201.31 \times 10^6$ per liter). A 33-year-old male donor from the China Marrow Donor Program who had the unmuted CCR5 gene had a fully matched HLA type (A*02:23, 33:03; B*49:01, 58:01; C*03:02, 04:03; DRB1*03:01, 11:01; and DQ*02:01, 03:01). On July 9, 2017, the patient underwent an allogeneic hematopoietic stem-cell transplantation after myeloablative conditioning with cyclophosphamide at a dose of $300 \text{mg}$ per kilogram of body weight per day (on days $-4$ and $-3$) and total-body irradiation at a dose of $5.0 \text{Gy}$ per day (on days $-2$ and $-1$).

CD34+ HSPCs ($2.36 \times 10^8$ cells) were sorted with magnetic beads from mobilized peripheral-blood mononuclear cells from the donor and subsequently subjected to CRISPR editing of the CCR5 locus. Because of limitations in sorting efficiency, the CD34-depleted cells ($2.66 \times 10^{10}$ cells) contained residual CD34+ cells, which accounted for 28.8% of the total CD34+ cells (Table S1 in the Supplementary Appendix). Both CCR5-edited CD34+ cells ($2.84 \times 10^8$ cells per kilogram) and unedited CD34-depleted cells ($3.21 \times 10^9$ karyocytes per kilogram) were infused into the patient. During the transplantation, the antiretroviral drug lopinavir–ritonavir was replaced by raltegravir (at a dose of 400 mg every 12 hours) to avoid drug interaction with cyclosporine. For prophylaxis against graft-versus-host disease, the patient received cyclosporine, a short course of methotrexate, basiliximab (an anti-CD25 antibody), and mycophenolate mofetil. Glucocorticoids and tacrolimus were used continuously for the treatment of graft-versus-host disease (Fig. 1A).

METHODS

STUDY OVERSIGHT

The study was designed to assess the safety and feasibility of the transplantation of CRISPR–Cas9–modified HSPCs into HIV-1–positive patients with hematologic cancer. Written informed consent was provided by the patient. The study was approved by the ethics committee of the 307 Hospital of the People’s Liberation Army in China. No commercial sponsor was involved. All experiments were performed in accordance with the protocol (available at NEJM.org). The study was designed by the last three authors. The manuscript was written and revised by the first, third, and last two authors and was approved by all the authors. The authors performed the data analysis and vouch for the completeness and accuracy of the data and for the adherence of the study to the protocol.

GENE EDITING AND PREINFUSION CELL PREPARATION

Mobilized peripheral-blood cells from an HLA-matched donor were separated on the basis of CD34 expression with the use of the CliniMACS system, following the manufacturer’s instructions. The sorted population was 95% CD34+ cells, equivalent to 71.2% of the total CD34+ cells (Table S1 in the Supplementary Appendix). Sorted
Figure 1. Engraftment of CCR5-Modified Cells.

The cell counts of white cells, neutrophils, and lymphocytes in peripheral blood over time are shown on the left y axis of Panel A, and the fluctuation in the hemoglobin level and platelet count are shown on the right y axis. The main preconditioning regimen contained cyclophosphamide (on days −4 and −3) and total-body irradiation (on days −2 and −1). The immunosuppression treatment included methotrexate (on days 1, 3, and 6), basiliximab (on days 0, 4, and 8), mycophenolate mofetil (initiated on day 0 and tapered from day 31 to 47), and cyclosporine (administered intravenously [IV] from day −1 to day 30 and orally from day 31 to 74). Graft-versus-host disease was treated with glucocorticoids (methylprednisolone or prednisone, administered intravenously from day 32 to day 124 and orally tapered from day 125 to 185) and tacrolimus (administered orally from day 75 to 156 and tapered from day 157 to 185). Antiretroviral therapy (ART) was interrupted from day 221 to day 249. The checkerboard design represents the tapering period. Panel B shows the CCR5 gene-disruption efficiency in bone marrow karyocytes detected by means of deep sequencing at different time points after transplantation. Panel C shows the CCR5 gene-disruption efficiency in various types of cells from peripheral-blood samples obtained 19 months after transplantation.
HSPCs were cultured in serum-free medium for 48 hours before transfection with a ribonucleoprotein complex comprising Cas9 protein and two previously designed guiding RNAs targeting CCR5. Gene-edited cells were cultured for 2 hours for recovery. CD34-depleted cells, the remaining mobilized peripheral-blood cells from the donor after the CD34 sorting, were transplanted with the edited CD34+ cells.

**Gene-Editing Assay**

Gene-editing efficiency was evaluated by means of Sanger sequencing and deep sequencing (3 million reads) of the genome of the recipient’s bulk bone marrow cells, CD34+ cells from bone marrow, peripheral-blood cells, and CD4+ cells from peripheral blood. To investigate the potential off-target effects of the CRISPR gene-editing system, whole-genome sequencing was performed on edited cells after genome editing and after engraftment.

**Results**

Recipient engraftment and acute lymphoblastic leukemia assay

Neutrophil and platelet engraftment occurred on days 13 and 27, respectively, after transplantation (see the Methods: Allogeneic Transplantation section in the Supplementary Appendix). Lymphocyte counts and T-lymphocyte subsets increased after transplantation, accompanied by the recovery of the CD4+ cell count to 592.94×10⁶ per liter in month 6 and its stabilization in a normal range (Table 1). Although the platelet count transiently decreased at month 3, the count spontaneously recovered and stabilized in a normal range (Fig. 1A). Full donor chimerism was achieved at week 4 after transplantation, and persisted through the most recent time point, 19 months after transplantation.

The acute lymphoblastic leukemia was in morphologic complete remission at week 4 after transplantation.  

Table 1. Key Laboratory Values before and after Transplantation.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Normal Range</th>
<th>Screening</th>
<th>3 Mo</th>
<th>6 Mo</th>
<th>9 Mo</th>
<th>12 Mo</th>
<th>15 Mo</th>
<th>19 Mo</th>
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<td>3.5–9.5</td>
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<td>4.89</td>
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<td>3.17</td>
<td>3.27</td>
<td>4.88</td>
<td>2.31</td>
<td>5.04</td>
<td>6.16</td>
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<td>1.22</td>
<td>2.02</td>
<td>3.28</td>
<td>3.25</td>
<td>4.11</td>
<td>3.27</td>
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<td>592.94</td>
<td>718.85</td>
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<td>3002.72</td>
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<td>63</td>
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<td>82</td>
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<td>20</td>
<td>32</td>
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<td>18</td>
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<td>Total bilirubin (µmol/liter)†</td>
<td>2–20</td>
<td>10.3</td>
<td>7.9</td>
<td>5.0</td>
<td>8.5</td>
<td>7.6</td>
<td>7.9</td>
<td>11.8</td>
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</table>

| Bone marrow values (%)‡         |                      |           |      |      |      |       |       |       |
| Blasts                          | <5                   | 2.0       | 0.5  | 0.5  | 0.5  | 2.0   | 1.5   |       |
| Minimal residual disease        | —                    | 0         | 0    | 0    | 0    | 0     | 0     |       |
| Chimeric ratio                  | >95                  | 99.56     | 99.83 | 99.74 | 99.56 | 100   | 100   |       |
| WT1–ABL                         | —                    | 0.085     | 0.173 | 0.053 | 0.368 | 0.041 | 0.034 | 0.463 |
transplantation; this remission continued over the 19-month follow-up period. In addition, minimal residual disease remained undetectable for leukemia-associated phenotypes on the basis of flow cytometry. The expression level of the Wilms’ tumor gene (WT1) normalized to the Abelson gene (ABL) — an increase in which predicts relapse — was less than 0.5% after transplantation, which was a level unchanged from before transplantation (Table 1).13,14

**CCR5 GENE EDITING**
The donor-derived, sorted HSPCs (CD34+ cells) were edited with the use of CRISPR–Cas9, resulting in CCR5 insertion or deletion (indel) efficiency of 17.8% as indicated by sequencing. In case the edited HSPCs did not result in long-term engraftment, the gene-edited HSPCs were transplanted with the CD34-depleted cells, which contained 28.8% of total CD34+ cells. Consequently, the proportion of CCR5 ablation in the genome of bone marrow karyocytes ranged between 5.20% and 8.28% during the 19-month long-term engraftment (Fig. 1B). The representative types of CCR5 gene mutation are shown in Figure S1 in the Supplementary Appendix. Deep sequencing was used to determine the gene-ablation efficiencies in multiple hematopoietic lineages, including CD4+, CD8+, CD19+, CD33+, and CD235a+ cells. CCR5 ablation was detected in multiple blood lineages, and a similar or slightly higher level of editing efficiency was observed in CD19+, CD33+, and CD235a+ cells, as compared with that in total peripheral-blood karyocytes (Fig. 1C). The levels of CCR5 ablation in CD4+ and CD8+ cells were not as high as in other cell subsets, possibly owing to the long-term persistence of T cells in the coinfused CD34-depleted cells.15 These results collectively showed that CRISPR-edited HSPCs successfully engrafted and differentiated into multiple lineages that retained the gene editing.

**SAFETY ANALYSIS**
The patient presented with predictable side effects after preconditioning, including anemia (hemoglobin level, 79 g per liter at day 22), neutropenia (undetectable neutrophils at day 0), and thrombocytopenia (platelet count, 12×10^9 per liter at day 6). No acute immune response was observed after the infusion of donor cells. Febrile neutropenia (grade 3) and bacteremia (Staphylococcus epidermidis; grade 3) developed in the first 2 weeks, which resolved with the use of standard antibiotic therapy. Acute graft-versus-host disease (of the skin; grade 1), urinary frequency and urgency (grade 2), cytomegalovirus viremia (grade 3), and herpes simplex reactivation occurred in month 2. Intermittent exotropia of the left eye, influenza-like symptoms, and an increased alanine aminotransferase level were observed successively from month 5 after transplantation to the latest time point of the follow-up. All these events resolved. No adverse events that were related to CCR5 gene editing were noted (Table S2 in the Supplementary Appendix).

To examine the off-target effects of the gene editing, we performed high-throughput genomewide sequencing at 100× coverage to analyze the genome of modified HSPCs that were sampled from the prerelease product. We first analyzed the previously predicted off-target site in our system (chr4:18476075–18476173); DNA cleavage was not detected at this site in this study.16 To identify other potential off-target sites, we used a computerized tool to predict 1997 loci to be candidates by comparing the two single-guide RNAs in our system with the human genome.16 Using the genomewide sequencing data, we excluded candidate sites with no indels near the prediction sites in modified HSPCs, with indels detected in the donor sample, or with previously identified indels, and we obtained 26 candidate sites including the 2 on-target loci (Table S3 in the Supplementary Appendix). We further performed deep sequencing to validate these 24 candidate off-target sites. Indels were detected in only 14 sites, which were all 1-bp length variance on nucleotide repeats and thus were not considered to be true off-target events.

To determine whether any off-target editing appeared after engraftment, we conducted a whole-genome sequencing assay on bone marrow blood samples that were obtained at week 15, month 12, and month 19 after transplantation. No off-target site was identified in any of these samples. Moreover, no chromosomal rearrangements or long-range deletions were identified in any of the four whole-genome sequencing data sets.

**MEASUREMENTS OF HIV-1 VIRAL LOAD**
Previous work has shown that the infusion of autologous CCR5-edited T cells may decrease the viral load in patients during a 4-week period of...
interruption of antiretroviral therapy. This finding suggests that CCR5 deletion may have the potential to mitigate the use of long-term antiretroviral therapy. To determine whether CCR5-edited stem cells could lead to an analogous benefit in our patient, an interruption of antiretroviral therapy was proposed. After we obtained a separate written informed consent from the patient, which was specifically related to the temporary cessation of antiretroviral therapy, a planned analytic interruption was performed 7 months after transplantation when the patient’s CD4+ cell count increased to a value in the normal range and the HIV RNA copies in plasma remained undetectable.

The serum viral load increased to $3 \times 10^7$ copies per milliliter at week 4 during the interruption of antiretroviral therapy, and the drugs were then resumed (Fig. 2A). The viral load gradually decreased to an undetectable level during the following months. During the interruption of antiretroviral therapy, the peripheral CD4+ cell count decreased from $575 \times 10^6$ per liter to $250 \times 10^6$ per liter, and the same trend was observed in the ratio of CD4+ cells to CD8+ cells. In addition, the level of CCR5 disruption in peripheral CD4+ cells before the interruption was 2.96%. The level of CCR5 disruption in CD4+ cells peaked (4.39%) during the interruption, at a level that was 1.6 times as great as the mean level, and was accompanied by a decrease in the CD4+ cell count (360×10^6 per liter). Moreover, immune-cell counts were evaluated before and after transplantation. CD4+ T-lymphopenia developed before transplantation, at which time the cell count was 201.31×10^6 per liter (Table 1), and the CD4+ cell count increased to a value in a normal range at month 6 after transplantation (Fig. 2C) and while the HIV-1 infection was under control with antiretroviral therapy.

To identify HIV tropism after transplantation, we tested peripheral-blood samples at months 8 and 19 after transplantation, and the virus tropism was still CCR5. In addition, the peripheral reservoir of HIV-1 was evaluated by the detection of HIV-1 DNA copies in peripheral CD4+ cells. The levels of total and integrated HIV-1 DNA were 734 and 72.5 copies per million CD4+ cells, respectively, after transplantation (Fig. S2 in the Supplementary Appendix). Their quick rebound after the interruption of antiretroviral therapy coincided with the appearance of a measurable viral load.

## Discussion

We report a successful allogeneic transplantation and long-term engraftment of CRISPR–Cas9–edited, CCR5-ablated HSPCs in a patient with HIV-1 infection and acute lymphoblastic leukemia. The donor cells engrafted with full chimerism, and the acute lymphoblastic leukemia was in complete remission for 19 months after transplantation, during which time the cells with the modified CCR5 gene persisted, and the CCR5 disruption ranged from 5.20 to 8.28% in bone marrow cells (Fig. 1B). These results show the proof of principle that transplantation and long-term engraftment of CRISPR–Cas9–edited allogeneic HSPCs can be achieved; however, the efficiency of the response was not adequate to achieve the target of cure of HIV-1 infection.

CRISPR-mediated CCR5 ablation efficiency was 5.20 to 8.28% in bone marrow samples over the 19-month follow-up period (Fig. 1B), and CRISPR-mediated CCR5 ablation was observed in multiple hematopoietic lineages (Fig. 1C), which shows the successful long-term engraftment of CCR5-ablated HSPCs in the patient. In particular, CD4+ cells with CCR5 indels were continuously produced and released into peripheral blood (Fig. 2C), and peripheral-blood CD4+ cell counts gradually recovered to the normal range in month 6 after transplantation while the patient was receiving treatment for HIV-1 infection (Fig. 2B), thus providing the patient with protection from opportunistic infection.

An important aspect of our study was the evaluation of the clinical safety of CRISPR–Cas9–mediated gene therapy. Previous HSPC-based gene therapies were less effective because of random integration of exogenous DNA into the genome, which sometimes induced acute immune responses or neoplasia. In our study, Cas9 ribonucleoprotein was introduced by means of nonviral transfection in order to avoid the introduction of exogenous DNA and avert the long-term existence of Cas9 in targeted cells, which was a potential causative factor for unexpected off-target indels. Using a high-throughput whole-genome assay to survey the pretransplantation sample as well as the samples obtained at 15 weeks, 12 months, and 19 months after transplantation, we did not detect any single-nucleotide variants, large deletions, or chromosomal rearrangements related to CRISPR modification. In addition, no evidence of gene-editing–related adverse events
was observed (Table S2 in the Supplementary Appendix). The apparent absence of clinical adverse events from gene editing and off-target effects provided preliminary support for the safety of this gene-editing approach. However, the current low efficiency of $CCR5$ targeting limited the depth of the off-target gene-editing analysis. It will be necessary to analyze the safety of CRISPR–Cas9–mediated $CCR5$ ablation in HSPCs further under a higher gene-targeting efficiency.

When antiretroviral therapy was interrupted at 7 months after transplantation, a small increase in the percentage of $CCR5$ indels was observed 2 weeks after the initiation of the interruption (Fig. 2C). The low efficiency of gene editing in the patient may be due to the competitive engraftment of the coinfused HSPCs in CD34-depleted

Figure 2. Clinical Outcomes during and after the Interruption of Antiretroviral Therapy.

Shown are the results of assessments for viral load (Panel A), the CD4+ cell counts and the ratio of CD4+ cells to CD8+ cells (Panel B), and the $CCR5$ gene-disruption efficiency in CD4+ cells (Panel C) from month 3 to month 12 after transplantation. Antiretroviral therapy was interrupted from day 221 to day 249.
cells and the persistence of donor T cells. To further clarify the anti-HIV effect of CCR5-ablated HSPCs, it will be essential to increase the gene-editing efficiency of our CRISPR–Cas9 system and improve the transplantation protocol.

A recent study showed that homozygosity for CCR5-A32 mutation is associated with a reduced life expectancy, which highlights the potential deleterious effect of CCR5 mutation at the individual level. However, unlike other gene-editing strategies that have been proposed for the management of HIV infection, CCR5 ablation within the hematopoietic system of infected persons will not alter expression in nonhematopoietic tissues. In conclusion, our study described the long-term engraftment of CCR5 CRISPR-edited CD34+ cells after allogeneic stem-cell transplantation, which gave rise to less than 8% gene disruption in the genome of circulating bone marrow cells, and off-target effects of the gene editing were not noted.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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