ORIGINAL ARTICLE

Hematopoietic Stem-Cell Gene Therapy for Cystinosis

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ABSTRACT

BACKGROUND

Cystinosis is a multisystemic lysosomal storage disorder caused by pathogenic variants in *CTNS*, the gene encoding cystinosin, a lysosomal transmembrane cystine transporter. In patients with cystinosis, cystine accumulates within lysosomes in all organs. The cystine-depleting agent cysteamine delays but does not prevent disease progression.

METHODS

In this phase 1–2, open-label, ongoing clinical study, we performed a preliminary assessment of CTNS-RD-04, which consists of autologous CD34+ cells transduced with lentiviral vectors carrying *CTNS* complementary DNA, in patients with cystinosis. The primary end points were the safety and the side-effect profiles of CTNS-RD-04. Secondary end points were measures of efficacy, including white-cell cystine levels and cystine storage depletion. Oral cysteamine was withdrawn before CTNS-RD-04 infusion, and cysteamine eyedrops were withdrawn 1 month after myeloablation.

RESULTS

Six participants (20 to 46 years of age) received CTNS-RD-04 and were followed for 29 to 63 months. CTNS-RD-04 doses ranged from 3.63×10^6 to 9.59×10^6 CD34+ cells per kilogram of body weight, and vector copy numbers ranged from 0.59 to 2.91 copies per diploid genome. All the patients had sustained and highly polyclonal hematopoietic reconstitution; vector copy numbers at 24 months ranged from 0.51 to 2.67 copies per diploid genome. A total of 217 adverse events occurred, most of which were mild or moderate in severity and largely consistent with the procedures and underlying disease. No evidence of monoclonal expansion was noted. White-cell cystine levels decreased from baseline except in Patient 4, who had the lowest vector copy number.

CONCLUSIONS

In this small study, CTNS-RD-04, an ex vivo gene therapy for cystinosis, had adverse effects that were largely consistent with the myeloablative regimen and underlying disease profile. White-cell cystine levels decreased after therapy. (Funded by the California Institute for Regenerative Medicine and others; ClinicalTrials.gov number, NCT03897361.)

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Cystinosis is a rare autosomal recessive lysosomal storage disease that places a tremendous burden on patients and caregivers and has poor outcomes, despite the availability of cystine-reducing treatment with cysteamine.[1] The disease is caused by pathogenic variants or deletions in the ubiquitous gene *CTNS* (17p13.2), which encodes cystinosin, a lysosomal transmembrane cystine transporter, and leads to the accumulation of cystine within lysosomes and cystine crystals within tissues.[2-5] Three allelic forms of cystinosis exist, the most severe and most common of which is the infantile form (Online Mendelian Inheritance in Man number, 219800). Renal Fanconi's syndrome develops in affected children by 6 to 18 months of age, and chronic kidney disease (CKD) eventually leads to end-stage kidney disease (ESKD).[2] Nonrenal complications of cystinosis include photophobia and corneal erosion,[3] cardiovascular complications,[4] diabetes mellitus,[5] hypothyroidism,[5] bone deformities and fragility,[6] neurologic defects,[7] and progressive myopathy that can result in life-threatening respiratory dysfunction, dysphagia, and aspiration pneumonia.[8,9]

Intracellular cystine reduction with the cystine-depleting agent cysteamine allows cystine to exit cells and slows the progression of the disease. To reduce corneal cystine crystal accumulation, cysteamine eyedrops are needed every hour during the time the person is awake. Premature death is inevitable, despite these therapies.

Given these issues, delivery of functional cystinosin to tissues throughout the body would be an important therapy. In preclinical studies in a rodent model of cystinosis, *Ctns*$^{-/-}$ mice,[10,11] we showed that transplantation of hematopoietic stem and progenitor cells (HSPCs) expressing functional *Ctns* resulted in tissue integration of bone marrow–derived cells, in decreased cystine accumulation, and in long-term preservation of kidney, thyroid, and eye function.[12-15] A mechanistic study in this model showed cross-correction through tunneling nanotubes, which appear to act as cellular bridges that support bidirectional lysosomal exchange between the tissue-engrafted HSPC-derived macrophages and microglia and the host's diseased cells.[12,13,16,17]

Allogeneic hematopoietic stem-cell transplantation is associated with considerable risk of complications and death; indeed, in one report, the death of a patient with cystinosis who underwent allogeneic hematopoietic stem-cell transplantation was considered to be related to graft-versus-host disease.[18] To avoid such an outcome, we developed an autologous transplantation strategy involving autologous gene-modified HSPCs and a self-inactivating lentiviral vector containing *CTNS* complementary DNA (cDNA) encoding functional cystinosin that had shown efficacy in *Ctns*$^{-/-}$ mice.[19] We now report the initial results of a phase 1–2, open-label clinical study of investigational gene therapy for cystinosis that involved the use of CD34+-enriched HSPCs transduced ex vivo with a self-inactivating lentiviral vector and contained *CTNS* cDNA (CTNS-RD-04) encoding functional cystinosin.

METHODS

STUDY DESIGN AND OVERSIGHT

We assessed the safety and efficacy of the CTNS-RD-04 drug product in six adult patients who had infantile cystinosis. Our ongoing study is being conducted at a single site at the University of California, San Diego; more complete descriptions are provided in the Supplementary Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org. In the primary clinical study, the patients were followed for 2 years and then were offered enrollment in an ongoing 13-year long-term follow-up study.

The study was designed by the principal investigators and coinvestigators. The first and last authors wrote the initial version of the manuscript, and all the authors participated in the interpretation of the data, the critical review of the manuscript, and the decision to submit the manuscript for publication. The authors who had access to the data vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. There was no confidentiality agreement between the sponsor and the authors or affiliated institutions. Novartis provided financial support for the database and long-term patient follow-up and was not involved in the study itself.

DRUG-PRODUCT MANUFACTURING AND INFUSION PROCEDURES

Before the drug-product infusion, patients received conditioning with busulfan with a target area under the curve (AUC) of 85 to 90 mg per liter

per hour, a dose selected because it provides an effective level of myeloablation with an acceptable side-effect profile.[23] Oral cysteamine treatment was discontinued 2 weeks before myeloablation conditioning with busulfan, and cysteamine eyedrops were discontinued 1 month after such conditioning; CTNS-RD-04 was infused intravenously.

To obtain CD34+ HSPCs, each patient underwent leukapheresis, and CD34+ HSPCs were selected after mobilization with granulocyte colony-stimulating factor, administered for 4 days, and plerixafor, administered for 1 day. Positive selection of CD34+ cells was performed before lentiviral vector transduction. In the course of this study, two different lentiviral vectors were used to generate a CTNS-RD-04 product, the pCCL-CTNS vector (for use in Patients 1, 2, and 3) and the pCDY-CTNS vector (for use in Patients 4, 5, and 6), the latter to prepare for transition to a commercially compatible vector (Supplementary Methods and Fig. S1 in the Supplementary Appendix). To improve the efficiency of lentiviral transduction, LentiBOOST (Revvity, formerly Sirion Biotech) at a dose of 1 mg per milliliter was added to the clinical manufacturing process during the transduction step for Patients 5 and 6. The minimum target yield for the drug product was 3×10^6 CD34+ cells per kilogram of body weight. Intravenous cell infusion was performed through the use of a customized administration setup after a 24-hour busulfan washout period. All the patients were closely monitored in the hospital for safety throughout conditioning, infusion, and hematologic reconstitution.

END POINTS

The patients attended regular follow-up visits at which blood samples were obtained and the patients were assessed for adverse events and disease progression (see the study protocol, available at NEJM.org). The primary end points were the safety and side-effect profiles of the drug product, as measured by the incidence and grade of adverse events and serious adverse events. Safety primary end points also included detection of replication-competent lentiviral or clonal expansion according to vector-integration site analysis; results were considered abnormal when a single site constituted more than 20% of the total integrations on two separate occasions.

We evaluated efficacy, as manifested by a reduction in white-cell cystine levels, an accepted marker of control of cystinosis, and granulocyte cystine levels, a newer method for measuring cystine content in peripheral blood, as secondary end points. Other efficacy end points included engraftment of the genetically modified HSPCs, as determined by the vector copy number and *CTNS* expression in peripheral-blood mononuclear cells. Intracellular cystine content was assayed in mixed white cells, isolated granulocytes, and rectal- and skin-biopsy samples (details are provided in the Supplementary Methods section in the Supplementary Appendix). Cystine crystals were quantified in rectal- and skin-biopsy samples on histologic sections prepared as described previously.[20] To obtain a normalized confocal crystal volume, we used the noninvasive intradermal confocal microscopy technique to quantify cystine crystals in the skin.[21] Corneal crystals were visualized by means of in vivo corneal confocal microscopy and density scored in deidentified micrographs, as described previously[22]; vision assessments were also performed. In addition, the patients evaluated photophobia, which they rated on a scale of 1 to 5, with 1 indicating no photophobia and 5 indicating severe photophobia. We calculated the estimated glomerular filtration rate (eGFR) using cystatin C and serum creatinine values with both the 2021 CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation and the 2021 CKD-EPI creatinine–cystatin equations. Neuromuscular and bone assessments and assessments of thyroid function (thyroxine and thyrotropin levels) and respiratory and cardiac function were performed. Neurocognitive evaluation was performed with the use of the Wechsler Abbreviated Scale of Intelligence, and evaluation of visual and motor coordination was performed with the Beery–Buktenica Developmental Test of Visual-Motor Integration, 6th Edition.

STATISTICAL ANALYSIS

This study was designed as a preliminary assessment of safety (primary end point) and white-cell cystine levels and other aspects of efficacy (secondary end points) of gene therapy for cystinosis. All results are provided descriptively, given the small patient cohort. No separate statistical analysis plan was developed.

Table 1. Demographic Characteristics of the Patients.*

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age at symptom onset or diagnosis	8 mo	6 mo	4 yr	6 yr	8 mo	2 yr
Age at time of CTNS-RD-04 treatment	20 yr	46 yr	22 yr	33 yr	31 yr	30 yr
Date of CTNS-RD-04 treatment	October 2019	June 2020	November 2020	November 2021	March 2022	October 2022
Sex	Male	Male	Male	Male	Female	Male
Pathogenic variant	57-kb deletion, nt1035(ins C), p.Val233Argfs*63	57-kb deletion, c.473t→C, p.Leu158Pro	c.18_21del, p.Thr7Phefs*7, c.295_298del, p.Val99Ilefs*18	57-kb deletion, c.473T→C, p.Leu158Pro	57-kb deletion, c.414G→A, p.Trp138*	Homozygous 57-kb deletion
Kidney transplantation status (yr)	Stage 3 CKD moderate at enrollment; 1 kidney transplantation 34 months after CTNS-RD-04 treatment (2022)	2 kidney transplantations (1987 and 1999)	1 kidney transplantation (2010)	2 kidney transplantations (2008 and 2017)	No kidney transplantation; stage 3 CKD moderate at enrollment	2 kidney transplantations (2010 and 2019)

* CKD denotes chronic kidney disease.

RESULTS

PATIENTS AND TREATMENT

Six patients, five men and one woman, who were between 20 and 46 years of age, were enrolled from July 2019 through May 2022 and received CTNS-RD-04. The demographics and vital signs of the patients are summarized in Table 1 and Tables S1, S2, and S3. The representativeness of the patients as compared with the broader population of patients with cystinosis is shown in Table S1. Two additional potential participants were excluded — one during screening owing to poor pulmonary function and one during leukapheresis owing to poor mobilization and unsatisfactory stem-cell collection. Although our small cohort limited generalizability, the characteristics of the patients aligned with those of adult patients with cystinosis eligible for advanced therapies. Two of the six patients had stage 3 CKD and had not yet undergone kidney transplantation, one had received a kidney transplant, and three had received two kidney transplants before stem-cell infusion. All six patients were receiving oral cysteamine, with a mean pill burden of 35.8 pills per day (Table S4). The present analysis, from July 2019 through January 2025, marked the end of the parent study (at least 24 months of follow-up for all the patients) and a 5-year follow-up for Patient 1, with a median follow-up of 36 months (range, 29 to 63). Five of the six patients enrolled in the long-term follow-up study; Patient 2 declined.

The AUC for busulfan conditioning ranged from 81.8 mg per liter per hour to 90 mg per liter per hour (Table S2). One day after busulfan conditioning, the patients received infusions of the CTNS-RD-04 product, which contained 3.63×10^6 to 9.59×10^6 CD34+ cells per kilogram, with a vector copy number of 0.59 to 2.91 copies per diploid genome (Table S2). LentiBOOST was introduced to the clinical manufacturing process during the transduction step in Patient 5 owing to transduction efficiency falling below the release criteria of the drug product (vector copy number, 0.4). Small-scale studies with CD34+ cells from Patient 5 confirmed that transduction efficiency was low, irrespective of the cell density, whereas adding Poloxamer 338 (research-grade LentiBOOST) was associated with a higher vector copy number (Table S5). LentiBOOST was subsequently used to manufacture the drug product for Patient 6 to proactively mitigate the risk of a low vector copy number in the resulting drug product. After mobilization, the CD34+ cell yield was low for Patients 4 and 6, who required repeated leukapheresis; Patient 6 had two drug products manufactured that were infused sequentially the same day (Table S2). After the infusion, all the patients reached absolute neutrophil and

platelet counts considered to constitute engraftment at a median of 13 days and 19.5 days, respectively (Fig. S2).

SAFETY (PRIMARY END POINT)

As of the data cutoff on January 30, 2025, a total of 217 adverse events had occurred, most of which were mild (178 events) or moderate (35 events) in severity and consistent with known risks associated with preinfusion conditioning, therapy after conditioning, and the underlying cystinosis and preexisting conditions (Table 2 and Tables S6 and S7). None of the adverse events appeared to be related to CTNS-RD-04. Four severe adverse events were identified: appendicitis in Patient 1, two episodes of worsening CKD in Patient 1, and preexisting coronary artery disease in Patient 6, which was also classified as a serious adverse event because it led to hospitalization for mitral-valve surgery (Table 2). Patients 1, 4, and 6 had thrombocytopenia at baseline (Fig. S2); the cause was unclear but presumably it was attributable to underlying cystinosis.[24] Patients 4 and 5 became infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at 10 weeks and 13 weeks, respectively, after the infusion of CTNS-RD-04, tested positive by polymerase-chain-reaction assay and antigen testing for 14 and 23 days, and had delayed white-cell reconstitution, with white-cell counts in the normal range at 9 months and 30 months, respectively, after infusion (Fig. S2).

BIOMARKERS

Vector Integration and Gene-Modified Cell Engraftment

Distributions of vector integration sites in patients' peripheral-blood mononuclear cell DNA at various time points showed highly polyclonal profiles, without evidence of monoclonal expansion or leukoproliferative complications. No unusual frequency of integration in or near cancer-associated genes was noted. The total number of unique vector integration sites across all the patients was between 396 and 85,868, with a mean of 12,640 unique sites (Fig. S3). We inferred that the difference in vector copy number ranging from 0.4 to 2.5 includes a range in terms of the integration number. The vector copy numbers showed long-term sustained stem-cell engraftment in peripheral blood ranging from 0.46 to 2.89 at 6 months and from 0.51 to 2.67 at 24 months (Fig. 1A). *CTNS* expression in the patients' peripheral blood increased from baseline, with a range from 11 times as high as baseline to 49 times as high as baseline at 24 months (Fig. 1B). The results for tissue engraftment of HSPC-derived cells as measured by gene marking in colon-biopsy samples (a secondary end point) is shown in Figures S4A and S4B.

Cystine and Cystine Crystals

At 24 months after infusion, white-cell cystine levels had decreased by 25 to 86% in all the patients; granulocyte cystine levels had decreased from preinfusion levels by 22 to 81% in five of the six patients (Fig. 2A and 2B and Fig. S5A). Patients 4 and 5, who had the lowest vector copy numbers, had the least reduction in cystine levels, and low-dose cysteamine (<25% of the original dose) was restarted at 36 and 14 months, respectively (Table S2). From baseline to the last rectal biopsy, three patients had reductions in crystal number and cystine content (Fig. S4C through S4E). Four patients had a reduction from baseline in the normalized confocal crystal volume, with Patient 3 having levels that were close to the levels of persons without cystinosis (Fig. S5B). Similarly, corneal confocal microscopy examinations showed decreased or stable cystine crystal density in the three patients in whom the test was performed (Fig. S6).

CLINICAL STATUS AND OUTCOMES (SECONDARY END POINTS)

Patient 1 had stage 3 CKD and stable eGFR until 12 months after the infusion; the eGFR then declined and the disease progressed to ESKD at 30 months after the infusion (Table S8). Patient 5 had stage 3 CKD and had a 47% decrease in eGFR, from 54 ml per minute per 1.73 m^2 at baseline to 25 ml per minute per 1.73 m^2 at 24 months after the infusion. Patient 5 had SARS-CoV-2 infection 13 weeks after the infusion and slow white-cell recovery with low monocytes that was possibly related to the steep decline in eGFR. Patients 2, 3, and 6, who had previously undergone kidney transplantation, had stage 2 CKD, and Patient 4 had stage 3 CKD; the eGFR in these patients remained stable overall (Table S8).

Thyroxine levels were normal at baseline and remained stable in all the patients (Fig. S7A). Thyrotropin levels increased over the course of the study period in two patients, Patient 1 and

Table 2. Major Adverse Events.*

Category	Attribution and Time Point (No. of Events)	No. of Events	No. of Patients
Gastrointestinal		26	6
Vomiting	Gastric erosions at screening (1), plerixafor mobilization (1), busulfan conditioning (3), appendicitis after infusion (1), immunization reaction at follow-up (2)	8	4
Diarrhea	Plerixafor mobilization (5), busulfan conditioning (2), food poisoning after infusion (1), erythromycin at follow-up (1)	9	5
Constipation	Opioid after infusion (3)	3	2
Oral mucositis	Busulfan conditioning (6)	6	6
Hematologic		20	5
Thrombocytopenia	Busulfan conditioning (7)	7	5
Leukopenia	Busulfan conditioning (4)	4	4
Neutropenic fever	Busulfan conditioning (5)	5	4
Epistaxis	Busulfan conditioning (3), mild trauma at follow-up (1)	4	3
Renal or electrolyte		18	4
Increased creatinine, BUN, chloride and decreased bicarbonate, potassium, phosphorus	CKD at screening (4) and after infusion (2), Fanconi's syndrome at screening (1) and after infusion (1), acyclovir and sulfamethoxazole–trimethoprim after infusion (1), plerixafor mobilization (1), busulfan conditioning (2), tacrolimus after infusion (2)	14	4
Hypomagnesemia	Apheresis mobilization (3), tacrolimus after infusion (1)	4	3
Endocrine		15	6
Azoospermia	Cystinosis at screening (5)	5	5
Gonadal failure	Busulfan conditioning (6)	6	6
Hypothyroidism	Cystinosis after infusion (1), cystinosis at follow-up (3)	4	4
Constitutional		14	5
Anorexia	Eosinophilic esophagitis at screening (1), busulfan conditioning (1), appendicitis after infusion (1), constipation after infusion (1), immunization reaction at follow-up (1)	5	2
Fatigue or lethargy	Apheresis mobilization (1), stress and anxiety at mobilization (1), busulfan conditioning (4)	6	5
Unintentional weight loss	Eosinophilic esophagitis at screening (1), appendicitis at follow-up (1), Covid-19 at follow-up (1)	3	2
Dermatologic		13	6
Alopecia	Busulfan conditioning (6)	6	6
Rash	Tape sensitivity at mobilization (1), PICC dressing after infusion (1), folliculitis after infusion (2), dermatitis after infusion (1), sulfamethoxazole–trimethoprim after infusion (1), vancomycin after infusion (1)	7	6
Swelling		5	2
Edema	Renal insufficiency after infusion (2)	2	2
Swelling of leg, arm, or knee	Popliteal cyst after infusion (1), intravenous infiltration at follow-up (1), mild trauma at follow-up (1)	3	2
Infection		3	3
Covid-19	Covid-19 after infusion (1), Covid-19 at follow-up (2)	3	3
Cardiac		1	1
Mitral-valve surgery†	Manifestation of preexisting valvular calcification at follow-up (1)	1	1

* A total of 217 individual events were recorded, of which the table enumerates the 115 most important, categorized according to system, with the times at which the events arose. The times during which adverse events were reported were screening, mobilization, conditioning, after drug-product infusion (defined as ≤90 days), and follow-up (defined as >90 days). The majority of events (71%) occurred during the mobilization, conditioning, and postinfusion periods. Of the adverse events, 178 were mild, 35 were moderate, 4 were severe, and 1 was serious. BUN denotes blood urea nitrogen, Covid-19 coronavirus disease 2019, and PICC peripherally inserted central catheter.

† This event was the only serious adverse event.

Patient 6 (Fig. S7B). Overall, vision assessments in the patients remained unchanged from baseline, and photophobia stabilized or decreased in all the patients except for Patient 5, who had reported a score of 4 for photophobia at baseline and a score of 5 at 30 months after infusion (Table S9).

All six participants had a normal neurologic examination at follow-up, with no evidence of weakness or oromotor dysfunction. Finger tapping, a measure of motor speed, remained stable in all the patients. Visual motor integration and visual perception remained stable; motor coordination, which was below average at baseline, improved modestly to a score within the normal range (Fig. S8A through S8C). Measures of strength (motor examination, grip strength, and timed walking) and cognitive function were stable over time (Fig. S8D and Fig. S9).

Bone density remained stable after drug-product infusion in all the patients (Table S10). Pulmonary and cardiac functions were stable, except in Patients 3 and 5, who had decreased pulmonary diffusion capacity after infusion (Tables S11 and S12).

DISCUSSION

The interim analysis of this study involving six patients with cystinosis supports the safety of gene-modified autologous CD34+ cell transplantation, with findings that suggest an acceptable risk–benefit profile and support continued clinical development of CTNS-RD-04 for the treatment of

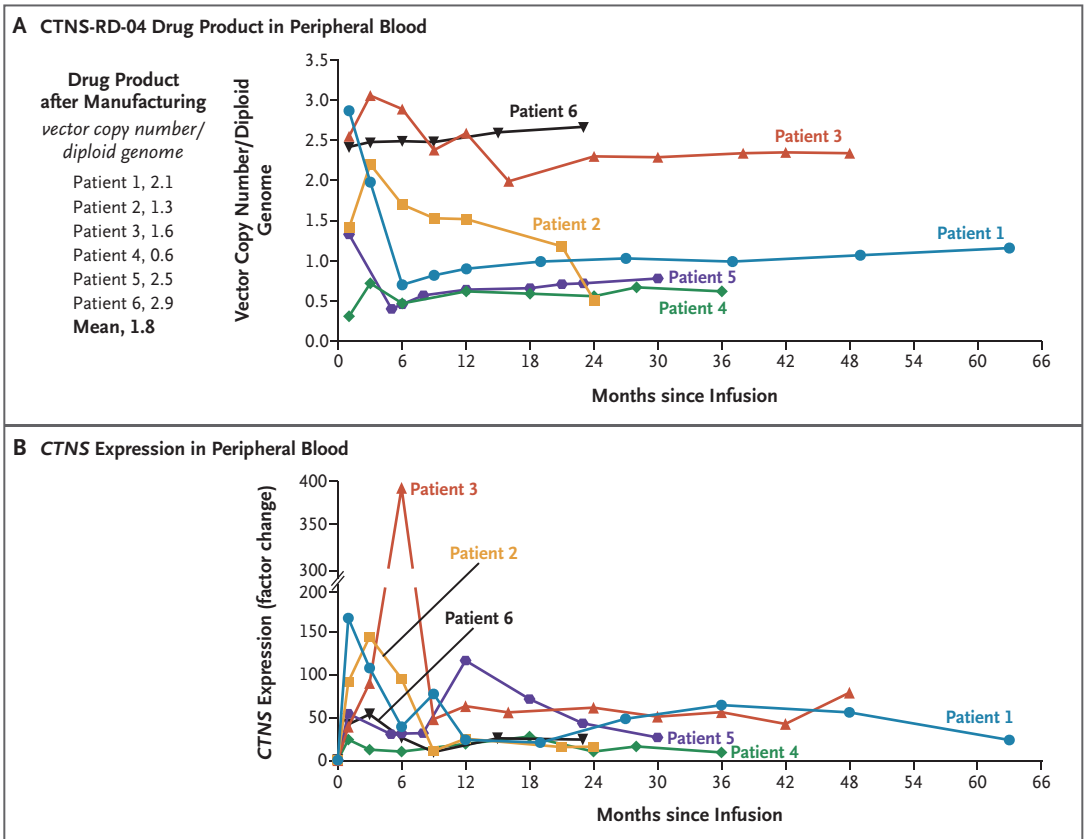

Figure 1. Vector Copy Number and *CTNS* Expression in Peripheral Blood over Time after Infusion.

Panel A shows the vector copy number in the CTNS-RD-04 drug product at the time of infusion and in peripheral blood at various times after infusion in each of the six patients. Patient 6 received two separate drug-product infusions, and the reported vector copy number represents the average of the two drug products. Panel B shows *CTNS* expression in the peripheral blood for each of the six patients at various times after infusion of CTNS-RD-04. For comparison, the mean *CTNS* expression in peripheral blood from three healthy donors was a factor change (±SD) of 2.97±0.65.

cystinosis. Evidence of sustained donor-cell engraftment was observed during follow-up (>5 years in one patient) with stable gene marking and *CTNS* expression in peripheral blood and tissues after infusion of CTNS-RD-04. None of the adverse events appeared to be related to CTNS-RD-04, and no fatal or life-threatening adverse events, clonal expansions, or leukoproliferative complications were reported. We interpret the results of our study to suggest that this approach may provide a therapeutic advance for patients with nephropathic cystinosis and suggest a need for additional study.

The peripheral-blood white-cell cystine level is an established surrogate marker for the diagnosis and therapeutic monitoring of cystinosis. A decrease in cystine levels was observed by both the classic mixed white-cell cystine assay and purified granulocyte cystine determination,[25] and results were associated with the vector copy number in the hematopoietic cell progeny. These results, along with those from longer follow-up periods, will be necessary to assess the therapeutic threshold of CTNS-RD-04 more completely.

Cystine crystal levels in the intestinal mucosa–biopsy samples, estimated with the method described previously by Dohil and colleagues,[20] were lower after gene therapy in three patients. A decrease from baseline in cystine crystals in the skin, as assessed by the intradermal confocal microscopy method,[21] occurred in four patients.

Assessment of the effects of CTNS-RD-04 on clinical outcomes in these six treated patients poses ongoing challenges owing to the diverse disease presentations in cystinosis. A report of 86 patients with cystinosis showed that among

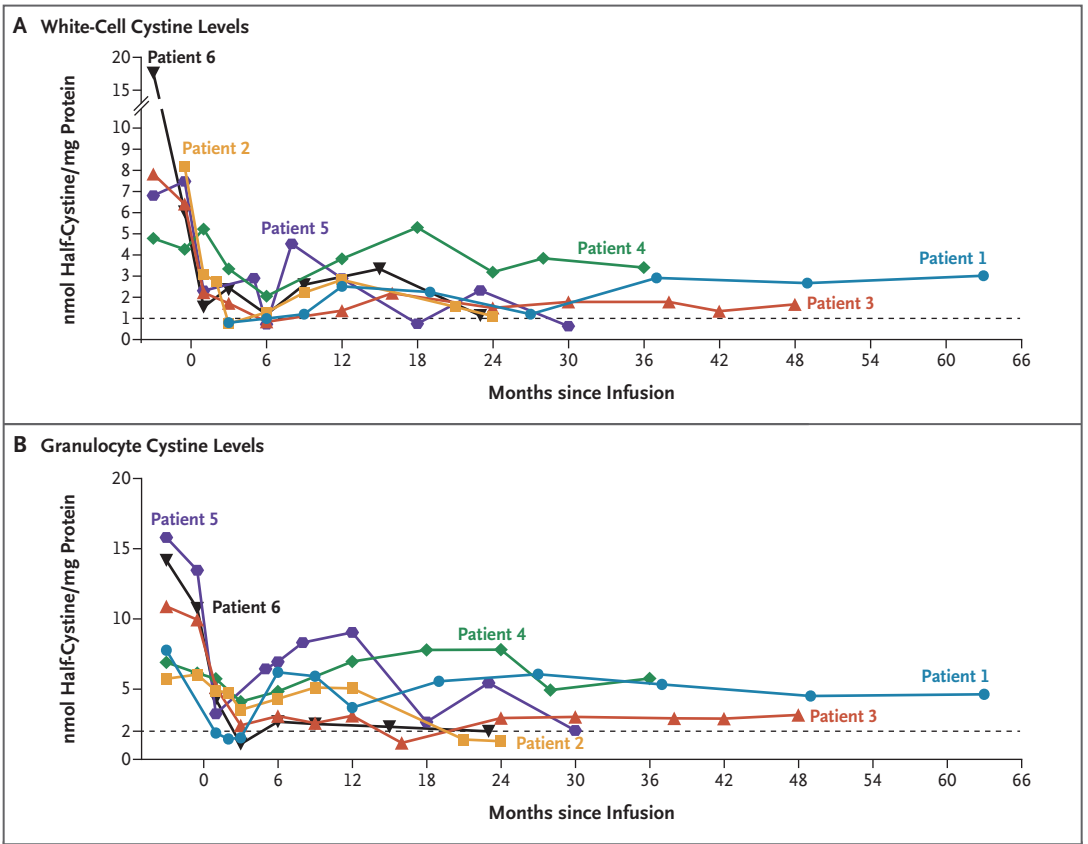

Figure 2. White-Cell Cystine Levels and Granulocyte Cystine Levels.

Panel A shows the white-cell cystine level at baseline and at various times after infusion. The white-cell cystine level was not measured at baseline in Patient 1. The therapeutic upper limit is indicated by the dotted line. Panel B shows the granulocyte cystine level at baseline and at various times after infusion. Patient 4 restarted oral cysteamine (150 mg per day) at 36 months after infusion. Patient 5 restarted oral cysteamine (450 mg per day) at 14 months after infusion.

patients who began receiving cysteamine before 5 years of age, ESKD still developed in 80% of the patients at a mean (±SD) age of 13.4±4.8 years.[26] Kidney function during the present study follow-up period was as anticipated — patients who had previously undergone kidney transplantation had stable kidney function, and those with preexisting advanced kidney disease had an expected decline.

Neurologic symptoms in patients with cystinosis include reduced gross and fine motor coordination, hypotonia, oromotor dysfunction, muscle weakness, and visual–spatial and visual–motor deficits, which do not abate over time.[7,27,28] In this study, the neuromotor and cognitive functioning of the patients remained stable over the entire period of observation and improved in some patients. After drug-product infusion, HSPCs have been shown to engraft in the central nervous system and differentiate into microglia-like cells in mice and humans.[29,30] We speculate that gene-modified HSPCs may lead to decreased cystine storage in the brain, resulting in improved motor coordination. With respect to peripheral nervous system involvement, patients with cystinosis present with distal vacuolar myopathy leading to progressive distal muscle wasting and weakness.[31] In the present study, grip strength remained generally stable or improved.

The ex vivo gene therapy approach reported here for cystinosis, a multisystem condition due to a transmembrane lysosomal protein variant, had adverse effects that were largely consistent with the myeloablative regimen and underlying disease profile and led to a reduction in white-cell cystine levels.

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

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