ORIGINAL ARTICLE

Base Editing of *HBG1* and *HBG2* Promoters for Sickle Cell Disease

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Abstract

BACKGROUND

Sickle cell disease is characterized by chronic hemolytic anemia and recurrent severe vaso-occlusive crises. Ristoglogene autogetemcel (risto-cel) includes autologous CD34+ hematopoietic stem and progenitor cells that have been base-edited to target the *HBG1* and *HBG2* promoters and inhibit BCL11A binding without altering BCL11A expression, yielding a switch in hemoglobin production from sickle hemoglobin (HbS) to antisickling fetal hemoglobin (HbF).

METHODS

In this phase 1–2 study, we enrolled patients 12 to 35 years of age with sickle cell disease who had had at least four severe vaso-occlusive crises in the 2 years before enrollment. After myeloablative conditioning with pharmacokinetically guided administration of busulfan, patients received a single infusion of risto-cel (at a dose of ≥3.0×10^6 viable CD34+ cells per kilogram of body weight). The primary efficacy end point was freedom from severe vaso-occlusive crises for 12 consecutive months, starting later than 60 days after the last red-cell transfusion. This interim analysis was unplanned; here, we describe safety, editing, engraftment, and hemoglobin production and the number of severe vaso-occlusive crises starting later than 60 days after the last red-cell transfusion.

RESULTS

A total of 31 patients received risto-cel and were followed for a mean of 6.6 months (range, 0.3 to 20.4). A median of one cycle (range, one to five) was required for stem-cell collection. Neutrophil engraftment occurred at a median of 17.5 days, and platelet engraftment at a median of 19 days. One patient died from idiopathic pneumonia syndrome. All 31 patients had at least one adverse event, 27 (87%) had an adverse event of grade 3 or higher, and 12 (39%) had a serious adverse event. At 6 months, the mean fraction of on-target edited alleles in peripheral blood was 67.4%, the mean HbF as a fraction of total hemoglobin was more than 60%, and the HbS as a fraction of total hemoglobin was less than 40% (among 13 patients); these levels were maintained throughout follow-up. No investigator-reported severe vaso-occlusive crises occurred later than 60 days after the last red-cell transfusion.

CONCLUSIONS

Treatment with risto-cel was followed by rapid engraftment and durable expression of HbF and reduction in HbS. These data support further investigation of risto-cel to treat sickle cell disease. (Funded by Beam Therapeutics; BEACON ClinicalTrials.gov number, NCT05456880.)

Sickle cell disease is a heteroge

nse mutations in *HBB*, the gene encoding β-globin, that lead to the production of abnormal sickle hemoglobin (HbS) with disrupted structure and function.[1-3] HbS polymerizes in the deoxygenated state, forming rheologically unfavorable sickle-shaped red cells with shortened lifespan.[4,5] The most common clinical manifestations of sickle cell disease are chronic hemolytic anemia and

recurrent severe vaso-occlusive crises, with progressive end-organ damage that causes substantial complications and early death.[4,6]

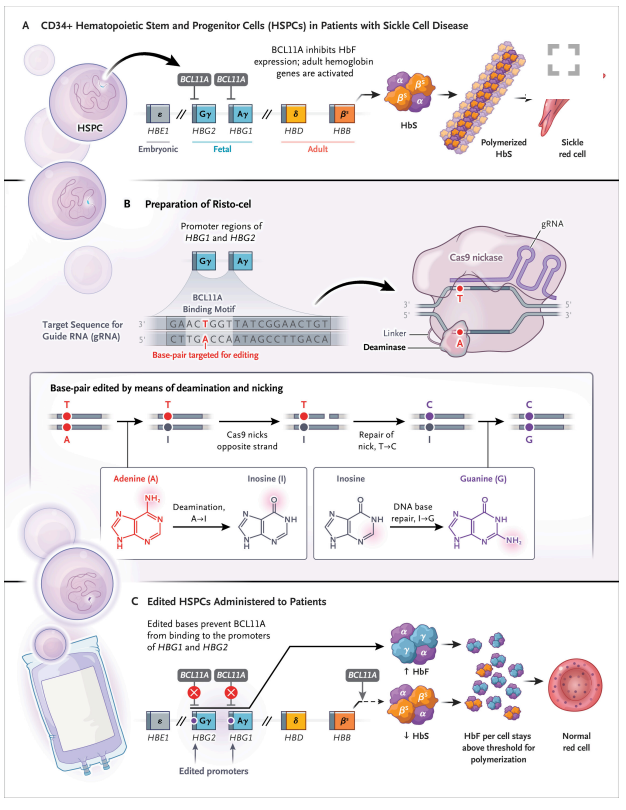
Allogeneic hematopoietic stem-cell transplantation provides a potentially curative option; however, fewer than 20% of persons in the United States have an optimally matched sibling donor available.[4-6] Furthermore, allogeneic hematopoietic stem-cell transplantation, along with conditioning-related toxic effects, is associated with a high risk of other treatment-related complications such as graft failure, potentially life-threatening infections, and graft-versus-host disease (for which prolonged immunosuppression is indicated).[4,7–9] Two autologous gene therapies, which involve gene insertion (by lentiviral vectors) and gene editing (with the use of clustered regularly interspaced short palindromic repeats [CRISPR]–CRISPR-associated protein 9 [Cas9]), were approved for the treatment of sickle cell disease and β-thalassemia in 2023.[10-12] A CRISPR-Cas12a gene-editing therapy targeting *HBG1* and *HBG2* is also under investigation for the treatment of these diseases.[13,14] Although these therapies offer transformative benefits, limitations include ongoing symptoms, alteration of the ratio of α-globin to β-globin with precipitation of excess β-like globin leading to ineffective erythropoiesis, and risks of insertional mutagenesis with lentiviral vector–based gene addition.[9,12] In the context of CRISPR-Cas9 nuclease gene editing, concerns include off-target genomic events, potential p53 activation by DNA double-strand breaks, and delayed platelet engraftment.[9,12]

Ristoglogene autogetemcel (BEAM-101; risto-cel) is an investigational genetically modified cell therapy consisting of ex vivo base-edited autologous CD34+ hematopoietic stem and progenitor cells (HSPCs) that are designed to increase the production of antisickling fetal hemoglobin (HbF) and decrease the production and levels of circulating HbS. HbF is the dominant hemoglobin during fetal development and early infancy.[15] The fetal-to-adult globin switch is mediated by transcriptional repressor BCL11A, which binds to regulatory sites within the *HBG1* and *HBG2* promoters and silences γ-globin expression, thereby reducing the production of HbF soon after birth.[15-17] Sustained pancellular expression of HbF into adulthood confers antisickling effects and is observed in persons with hereditary persistence of fetal hemoglobin (HPFH) who coinherit the sickle mutation.[18,19] Among patients with sickle cell disease, HbF levels of 10 to 20% are associated with improved childhood survival, whereas levels approaching those seen in persons with HPFH (30 to 40%) are linked to a markedly attenuated disease course.[20,21] Families with homozygous deletional HPFH, resulting from large deletions in the β-globin gene cluster and characterized by constitutively elevated HbF level, have HbF values ranging from 60 to 100%, and no adverse clinical effects have been described in the literature.[22-24] Protection against red-cell sickling is achieved under normal conditions at a concentration of 10 pg of HbF per F cell (a red cell that expresses detectable levels of fetal hemoglobin).[20,21]

The risto-cel editing process uses electroporation, a nonviral delivery system, to deliver an adenine base editor–encoding messenger and guide RNAs to HSPCs to introduce A-to-G substitutions in the *HBG1* and *HBG2* gene promoter regions. This process disrupts BCL11A binding sites and mimics the increased expression of HbF that is seen in HPFH (Figure 1, and see the Supplementary Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org).[25,26] Unlike other gene-therapy strategies, the risto-cel editing process directly targets the BCL11A binding site of the *HBG1* and *HBG2* promoters to inhibit BCL11A binding, without altering BCL11A expression. Our strategy, in which the *HBG1* and *HBG2* promoter BCL11A–binding site is disrupted to up-regulate HbF, preserves the normal expression of BCL11A and its roles in erythroid differentiation[17,27,28] and other lineages, such as lymphoid cells.[29-32]

Through the use of a Cas9 nickase and a base-editing enzyme, the risto-cel editing process generates precise and uniform edits, avoids insertions or gene rearrangements, and prevents p53 activation by precluding the formation of double-strand breaks.[33] In preclinical in vitro studies, risto-cel showed successful editing at more than 90% of the intended on-target allele sites (*HBG1* and *HBG2* promoters) in multilineage cells and more than 60% of the total hemoglobin was HbF induced by the edit, with a reduction in the HbS level (to <40%) in erythroid cells. In vivo studies in humanized mice have shown HbF expression of more than 60%, with durable allelic editing 16 weeks after transplantation.[29,30] We conducted the BEACON study to evaluate the safety and efficacy of risto-cel in patients with sickle cell disease and recurrent severe vaso-occlusive crises.

FIGURE 1



Mechanism of Action of Risto-cel.

Methods

STUDY DESIGN

In this ongoing phase 1–2, single-group, open-label study being conducted at 18 sites in the United States, we are evaluating the safety and efficacy of a single dose of risto-cel in patients with sickle cell disease and severe vaso-occlusive crises. Eligible patients were 12 to 35 years of age, with a documented diagnosis of sickle cell disease; an eligible genotype (β^S/β^S, β^S/β^0, or β^S/β^+); at least four severe vaso-occlusive crises, despite standard-care measures, in the 2-year period before the provision of informed consent; no available HLA-matched sibling donor; and no history of overt stroke. This clinical study offered fertility-preservation coverage to all patients before the initiation of busulfan-based conditioning.

After screening, eligible patients underwent a minimum of 6 weeks of simple or exchange transfusion therapy before mobilization with single-agent plerixafor, which was administered with the use of a weight-based approach (in patients with a body weight of >83 kg) or a fixed-dose approach according to weight tiers (in patients with a body weight of ≤83 kg).[34] To alleviate the mobilization-related treatment burden, up to 4 days were allowed per mobilization cycle.[35] Autologous CD34+ HSPCs were obtained by means of leukapheresis for up to 4 consecutive days per cycle and were genetically modified with an adenine base editor by means of a closed, automated manufacturing process that is specialized for sickle cell disease at the internal Good Manufacturing Practice facility of Beam Therapeutics.[36] After myeloablative conditioning with pharmacokinetically guided administration of busulfan (cumulative area-under-the-curve target, 80 hr·mg per liter [target range, 68 to 92]), risto-cel was administered as a single intravenous infusion, with a minimum cell dose of 3.0×10^6 viable CD34+ cells per kilogram of body weight.

Three patients were treated in the sentinel cohort. After approval by the data monitoring committee, additional patients were enrolled in the expansion cohort. Patients were monitored for neutrophil and platelet engraftment in the inpatient setting until the occurrence of neutrophil engraftment, with further monitoring until 24 months after transplantation. After completion of the 24-month study, participants who received risto-cel have the option to be enrolled in a 13-year long-term extension study. Additional details of the study methods are provided in the Supplementary Appendix and in the study protocol (available at NEJM.org).

STUDY OVERSIGHT

The study was sponsored by Beam Therapeutics and designed in collaboration with experts in the field and patient advocates. The study was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation, the principles of the Declaration of Helsinki, and all national, state, and local laws or regulations. Patient feedback was sought on the study design and educational materials. An external independent data monitoring committee monitored safety during the course of the study. Before study participation, all the adult patients provided written informed cons ent, which was accompanied by written informed consent from pleteness and accuracy of the data and for the adherence of the study to the protocol and statistical analysis plan (which is available with the protocol). All the authors had access to the study data after the data-cutoff date, reviewed the manuscript, and approved

it for submission for publication. Medical writing assistance was provided by a medical writer (funded by the sponsor) and by an employee of the sponsor.

END POINTS

The key safety end points were successful neutrophil engraftment, the time to neutrophil engraftment, the time to platelet engraftment, and transplantation-related death within 100 days after the risto-cel infusion. The primary efficacy end point was freedom from severe vaso-occlusive crises for at least 12 consecutive months, starting later than 60 days after the last red-cell transfusion, as adjudicated by the end-point adjudication committee. In this nonprespecified interim analysis, we report investigator-reported severe vaso-occlusive crises, which were not adjudicated by the committee. Sickle cell pain crises were defined as acute episodes of pain, with no medically determined cause other than a vaso-occlusive crisis that led to at least 24 hours of treatment in a hospital or observation unit or that led to a visit to an emergency department, urgent care facility, or outpatient facility involving therapy with an opioid or an intravenous or intramuscular nonsteroidal antiinflammatory drug. Severe vaso-occlusive crises included sickle cell pain crises, acute chest syndrome, priapism, or splenic sequestration crisis (see the protocol for full definitions).

Additional secondary and pharmacodynamic end points included adverse events, total hemoglobin levels, HbF and HbS levels, hemolysis markers, the percentage of F cells, and the percentage of gene editing at target alleles in peripheral-blood and bone marrow cells. The guide RNA is designed to target identical promoter regions of *HBG1* and *HBG2*, and the base editor Cas9 nickase can create two nicks on the same DNA strand with potential generation of a 4.92-kb deletion that includes *HBG2*. The frequency of this *HBG2* deletion in peripheral blood and bone marrow cells over time (exploratory analysis) was assessed by means of droplet digital polymerase chain reaction (ddPCR) to measure the percentage of deleted *HBG2* alleles (Fig. S2, and see the Methods section in the Supplementary Appendix). The *Medical Dictionary for Regulatory Activities*, version 28.0, was used to code all adverse events.

STATISTICAL ANALYSIS

This nonprespecified interim analysis was completed in order to update the scientific community regarding sickle cell disease treatment. The enrolled population included patients who provided written informed consent and met the inclusion and exclusion criteria. Analyses of safety and efficacy included all the patients who received risto-cel (the treated population). The target size of the study population (55 patients) was chosen to provide the study with at least 85% power, with a significance level of 2.5%, to rule out a 60% response among the study patients, when the true percentage of patients with a response is 80% among those who have not had any severe vaso-occlusive crisis for at least 12 consecutive months, as assessed starting later than 60 days after the last red-cell transfusion.

Results

PATIENT POPULATION

As of the data-cutoff date (August 6, 2025), enrollment was completed. Of the 54 patients who had been enrolled in the study, 50 started the mobilization process, 39 had the manufacture of the risto-cel dose completed, and 31 (30 adults and 1 adolescent) were treated with risto-cel (Fig. S1 in the Supplementary Appendix). The representativeness of the study population is discussed in Table S1. The demographic and clinical characteristics of the patients are shown in Table 1. Five patients withdrew or were discontinued from the study (Table S2). Of the 31 treated patients, 23 completed fertility preservation and 8 declined to do so (Table S3).

TREATMENT

Among the treated patients, a median of one cycle (range, one to five) was required for stem-cell collection, and the median number of total collection days for risto-cel manufacture was 3 (range, 1 to 13). A total of 20 patients (65%) had one mobilization cycle, 5 (16%) had two cycles, and 6 (19%) had three or more cycles. Among patients who completed stem-cell collection (42 patients total), 34 had a body weight of 83 kg or less; among these 34 patients, 7 received weight-based plerixafor and 27 received fixed-dose plerixafor. Patients who received fixed-dose plerixafor had a lower median number of collection cycles and total mobilization days than those in the weight-b

No manufacturing failures occurred. All the patients who completed mobilization had sufficient CD34+ cells for drug-product manufacturing that successfully met the dose, release, and testing criteria. The median

TABLE 1

time from the start of mobilization to drug-product release was 2.9 months (range, 2.2 to 7.8), and the median time from the start of mobilization to infusion was 4.5 months (range, 3.1 to 10.5). Treated patients received a median risto-cel dose of 6.2×10^6 viable CD34+ cells (range, 3.2×10^6 to 23.4×10^6) per kilogram. The mean (±SD) duration of follow-up was 6.6±5.1 months (range, 0.3 to 20.4).

SAFETY

Engraftment

Patients had neutrophil engraftment at a median of 17.5 days (range, 12 to 30) after the risto-cel infusion, with a median of 7 days (range, 1 to 17) of severe neutropenia, and had platelet engraftment at a median of 19 days (range, 11 to 53) (Table 2). The last peripheral red-cell transfusion after the risto-cel infusion was administered at a median of 14 days (range, 1 to 26). Nine patients had platelet engraftment without receiving a platelet transfusion, among whom six had platelet counts that did not fall below 50,000 per microliter, indicating rapid and robust platelet recovery.

Adverse Events

All 31 patients had at least one adverse event during the drug infusion or during the follow-up period after the infusion (Table 3); most of these events occurred within the first 12 weeks after the risto-cel infusion (Tables S6 and S7). A total of 27 patients (87%) had an adverse event of grade 3 or higher, and 12 patients (39%) had a serious adverse event (Table S8). No patient had any serious adverse event that was considered by the investigator to be related to risto-cel, and no patient had engraftment failure or cancer.

One patient died 4 months after the risto-cel infusion. After conditioning therapy with pharmacokinetically adjusted busulfan within the protocol target range, successful engraftment had occurred by month 2 after the risto-cel infusion (total hemoglobin level, 11 g per deciliter; HbF, 40.6%; and HbS, 14.5%), but the patient was hospitalized from days 58 to 82 for respiratory distress. Extensive workup was performed, which ruled out infection, hemorrhage, and other potential causes. The patient was initially discharged with a clinically stable condition, but the patient was readmitted 4 days later with worsening respiratory distress, acute lung injury, pneumomediastinum, and pneumothorax. The clinical course was consistent with post-transplantation idiopathic pneumonia syndrome, which ultimately resulted in death. Previous e-cigarette use (vaping) was later identified as a possible contributing factor. The investigator and independent data monitoring committee noted that this event was probably related to idiopathic pneumonia syndrome, a known noninfectious inflammatory lung injury that can occur after HSPC transplantation in the context of high-dose conditioning regimens, such as busulfan (Table S9).

EFFICACY AND BIOMARKER ANALYSES

Editing Characteristics

The mean fraction of on-target edited alleles in peripheral blood was 67.6±8.8% (range, 37.8 to 78.7) by 3 months (among 22 patients), 67.4±7.9% (range, 53.0 to 80.1) by 6 months (among 13 patients), and 72.8±3.2% (range, 69.2 to 77.6) by 12 months (among 5 patients) (Figure 2). The mean fraction of on-target edited alleles in bone marrow was 76.8% by 12 months among 4 patients. In nonclinical studies, off-target editing was seen in two extensi
not been observed in post-trans
protocol).

Table 1. Demographic and Clinical Characteristics of the Patients (Treated Population).*

Characteristic	Patients (N=31)
Age — yr	
Mean	22.8±4.7
Range	16–34
Sex — no. (%)	
Male	16 (52)
Female	15 (48)
Genotype — no. (%)†	
β^S/β^S	28 (90)
β^S/β^0	1 (3)
β^S/β^+	2 (6)
Race — no. (%)‡	
Black	25 (81)
White	1 (3)
Not reported	4 (13)
Other	1 (3)
Previous hydroxyurea use — no. (%)	31 (100)
Median no. of investigator-reported sVOCs in the 2-yr baseline period (range)	7 (4–60)

* Plus–minus values are means ±SD. The treated population included all the patients who had received ristogloogene autogetemcel (risto-cel). Percentages may not total 100 because of rounding. The term sVOC denotes severe vaso-occlusive crisis.
† The genotype β^S/β^S indicates a homozygous sickle cell genotype in which both β-globin alleles carry the sickle hemoglobin (HbS) mutation, β^S/β^0 a heterozygous genotype in which one allele carries the HbS mutation and the other carries a β^0-thalassemia mutation resulting in no β-globin production, and β^S/β^+ a heterozygous genotype in which one allele carries the HbS mutation and the other carries a β^+-thalassemia mutation resulting in reduced β-globin production.
‡ Race was reported by patients or their legal representatives.

Demographic and Clinical Characteristics of the Patients (Treated Population).

TABLE 2

Table 2. Mobilization, Collection, and Transplantation Characteristic Population).*

Variable	Patients (N=31)
Median no. of stem-cell collection cycles (range)	1 (1–5)
Total median no. of collection days for risto-cel manufacture (range)	3 (1–13)
Cumulative AUC for busulfan (range) — hr·mg/liter	71.0 (61.0–86.1)
Median risto-cel dose infused (range) — $\times10^{-6}$ viable CD34+ cells/kg	6.2 (3.2–23.4)
Duration of follow-up after risto-cel infusion — mo	
Mean	6.6±5.1
Range	0.3–20.4
Median no. of days to last red-cell transfusion after risto-cel infusion (range)†	14 (1–26)
Neutrophil engraftment — days‡	
Median time to neutrophil engraftment (range)	17.5 (12–30)
Median duration of severe neutropenia (range)§	7 (1–17)
Platelet engraftment	
Median time to platelet engraftment (range) — days¶	19 (11–53)
Platelet count ≥50,000/μl — no. (%)	6 (19)
Did not receive a platelet transfusion — no. (%)	9 (29)
No. of patients with transplantation-related death within 100 days after risto-cel infusion	0

* Plus–minus values are means ±SD. Mobilization refers to the pharmacologic induction of hematopoietic stem and progenitor cells to migrate from the bone marrow into the peripheral blood. AUC denotes area under the curve.
† One patient was excluded from this analysis. The patient received several red-cell transfusions up to 122 days after successful engraftment owing to an acute illness that resulted in death at 4 months after the infusion.
‡ A total of 28 patients had neutrophil engraftment by the data-cutoff date. Three patients had neutrophil engraftment after the data-cutoff date, at 17 days (in 2 patients) and at 21 days (in 1) after the risto-cel infusion.
§ Severe neutropenia was defined as an absolute neutrophil count of less than 500 cells per microliter.
¶ A total of 27 patients had platelet engraftment by the data-cutoff date. Four patients had platelet engraftment after the data-cutoff date, at 24 days (in 2 patients), 26 days (in 1), and 52 days (in 1) after the risto-cel infusion.

…ion, Collection, and Transplantation …ics (Treated Population).

NEW

TABLE 3

HBG2 deletion (assessed as the percentage of alleles containing the deletion, as measured by ddPCR) was evaluated in blood samples obtained from 22 patients at month 3, with a mean value of 1.4±1.5% (range, undetected to 3.6); it was also present, albeit at lower levels, at months 6, 12, and 18 in the samples in which the deletion was detected at 3 months (Table S10). We detected this deletion in bone marrow samples obtained from 5 patients at month 12, with a mean percentage of 1.8±0.5% (range, 1.4 to 2.4).

Hemoglobin and Other Blood Analyses

Patients' total hemoglobin levels increased from a baseline mean of 9.2±1.5 g per deciliter (range, 6.9 to 12.5) (among 31 patients) to a mean of 12.2±1.4 g per deciliter (range, 9.0 to 14.7) by month 1 (among 27 patients) and 15.5±2.0 g per deciliter (range, 11.9 to 18.6) by month 6 (among 13 patients) — levels that were sustained during follow-up (Figure 2). Elevated total hemoglobin levels that were above the upper limit of the normal range were observed in 4 patients beyond month 6 without any associated clinical manifestations or use of therapeutic interventions. An elevated hemoglobin level was not considered to be clinically meaningful, and no adverse events related to a high hemoglobin level were observed.

Mean (±SE) erythropoietin levels decreased from 83.0±18.6 mIU per milliliter (range, 12.3 to 555.9) at baseline (among 30 patients) to 27.2±4.1 mIU per milliliter (range, 7.9 to 50.1) at 6 months (among 11 patients) and 16.1±5.3 mIU per milliliter (range, 6.8 to 35.1) at 12 months (among 5 patients), findings consistent with a reduced hypoxic drive (Fig. S3). The rate of sickling and maximum induced sickling decreased after risto-cel infusion to levels similar to those seen in sickle cell trait reference samples (Fig. S4).[37,38]

The mean endogenous HbF fraction (calculated as HbF÷[HbF+HbS]) in circulating red cells was more than 60% and the mean HbS was less than 40% in nontransfused blood by month 1; these levels were sustained throughout follow-up. In total peripheral blood at month 6, the mean (±SD) percent of F cells was 99.3±0.8% (range, 97.0 to 99.9), with a mean of 20.6±1.7 pg of HbF per F cell (range, 18.0 to 23.9), a level that was well above the protective threshold against sickling (Figure 2). Markers of hemolysis (lactate dehydrogenase, indirect bilirubin, and haptoglobin levels and reticulocyte counts) normalized or decreased after the risto-cel infusion (Fig. S5).

Severe Vaso-Occlusive Crises

Among the 31 patients who received risto-cel, 13 had at least 6 months of follow-up. As of the data-cutoff date, no patient has had an investigator-reported severe vaso-occlusive crisis after engraftment (Figure 3).

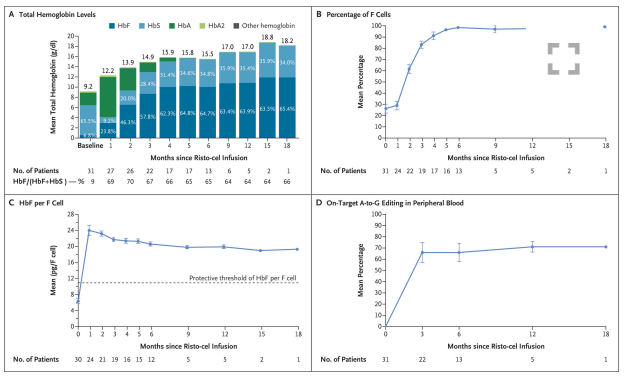
Table 3. Adverse Events after Risto-cel Infusion.*

Event	Pa (N = 31)
Any adverse event related to risto-cel†	3 (10)
Most common adverse events	
Stomatitis	24 (77)
Febrile neutropenia	22 (71)
Decreased appetite	10 (32)
Hypokalemia	10 (32)
Skin hyperpigmentation	10 (32)
Adverse events of grade ≥3 occurring in ≥2 patients	
Febrile neutropenia	17 (55)
Stomatitis	15 (48)
Decreased appetite	9 (29)
Platelet count decreased	6 (19)
Anemia	5 (16)
Neutrophil count decreased	4 (13)
Hypokalemia	3 (10)
Nausea	3 (10)
White-cell count decreased	3 (10)
Acute kidney injury	2 (6)
Hematuria	2 (6)
Hypoxia	2 (6)
Laryngeal inflammation	2 (6)
Pharyngeal inflammation	2 (6)
Pyrexia	2 (6)
Serious adverse events occurring in ≥2 patients	
Pain	2 (6)
Acute kidney injury	2 (6)
Death	1 (3)
Any adverse event leading to study discontinuation	0

* The *Medical Dictionary for Regulatory Activities*, version 28.0, was used to code all adverse events.
† Adverse events that were considered by the investigator to be related to risto-cel included cough, vomiting, and dyspnea (in one patient), muscle spasms and facial swelling (in one), and dizziness (in one). All the events related to risto-cel, except for muscle spasms and facial swelling, occurred on day 1. All the adverse events that were considered to be related to risto-cel were of grade 1 or 2 except one nonserious grade 3 allergic facial swelling 11 weeks after the infusion that resolved the same day and was assessed by the investigator as being possibly related to risto-cel.

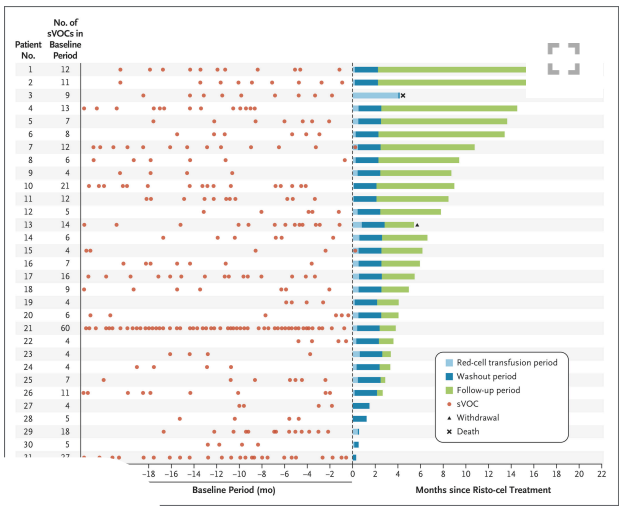
Adverse Events after Risto-cel Infusion.

FIGURE 2



Changes in Total Hemoglobin Levels, Pancellular HbF Distribution, and Peripheral Blood Editing.

FIGURE 3



NEW *Reported Severe Vaso-occlusive Crises after Treatment with Risto-cel (Treated Population).*

Discussion

In this ongoing study (BEACON), one-time treatment with risto-cel in 31 patients with up to 20 months of follow-up was followed by rapid engraftment and durable expression of HbF of more than 60% and reduction in HbS to less than 40%. One patient died from idiopathic pneumonia syndrome. Adverse events were generally consistent with busulfan conditioning, autologous hematopoietic stem-cell transplantation, and underlying sickle cell disease, a finding that underscores the importance that treating physicians ensure patient understanding of the overall risks of busulfan conditioning and transplantation and continue to counsel them throughout the study to avoid risk factors (such as smoking, vaping, and alcohol use) that could further elevate the risks of pulmonary and liver toxic effects that have been associated with busulfan conditioning.[39-41] Because this study is ongoing, the primary efficacy end point cannot be evaluated yet; as of the data-cutoff date for this analysis, no participant has had an investigator-reported severe vaso-occlusive crisis after engraftment.

In this analysis, a large proportion of HSPCs showed the intended edit, as indicated by high expression of HbF, reduced expression of HbS, and the ratio of HbS to non-HbS that is consistent with the sickle cell trait — findings that reflect predictable and uniform editing.[33,42] In nonclinical studies, off-target edits were observed at two sites; we would predict that these off-target edits would pose a low risk or no risk to patients because of their intronic location and lack of functional activity.[30,33] No off-target edits were observed in post-transplantation clinical samples. In addition, the deletion was observed in less than 4% of *HBG2* alleles in the blood or bone marrow (as measured by ddPCR); nonclinical analyses showed no impairment to erythroid differentiation or ability to produce HbF (data on file, Beam Therapeutics).

Rapid neutrophil and platelet engraftment was observed, which is consistent with results reported in allogeneic transplantation with unmodified cells.[43,44] Rapid engraftment has the potential to reduce the duration of hospitalization, limit transfusions, and hasten recovery from conditioning-related complications such as infection or mucositis, thereby enhancing safety and reducing the treatment burden on patients, families, and health care facilities.

An elevated total hemoglobin level after month 6 was observed at least once in four patients; three patients were young men (18 to 22 years of age) who were asymptomatic and without clinical manifestations. This finding was probably multifactorial, reflecting physiologic adaptation and compensatory erythrocytosis to maintain adequate oxygen delivery in the context of the increased oxygen affinity of HbF, together with an increased edited progenitor-cell population in risto-cel, improved red-cell lifespan, and the influence of other coexisting conditions and physiologic factors (e.g., preexisting obstructive sleep apnea and increased testosterone levels in men). Total hemoglobin levels remained stable or have normalized over time, and comprehensive evaluation showed no associated clinical manifestations, adverse events, or indication for therapeutic intervention.

Patients had rapid, robust, and pancellular HbF expression after treatment with risto-cel. Sickling kinetics decreased to levels similar to those of sickle cell trait reference samples. The resolution of anemia, sickling, and hemolysis that was seen in all patients is consistent with improved red-cell health and function. The BEACON study, however, is limited by the single-group design, a narrow age range for enrollment, the exclusion of patients with a history of stroke, restriction to a United States–based population, and limited applicability to the specific genotypes and age groups studied; the current analysis is limited by a short duration of follow-up.

NOTES

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REFERENCES

1. Galamba N. On the nonaggregation of normal adult hemoglobin and the aggregation of sickle cell hemoglobin. *J Phys Chem B* 2019;123:10735-10745.

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2. Mandal AK, Mitra A, Das R. Sickle cell hemoglobin. *Subcell Biochem* 2020;94:297-322.

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3. Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle cell disease. *Lancet* 2017;390:311-323.

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4. White SL, Hart K, Kohn DB. Diverse approaches to gene therapy of sickle cell disease. *Annu Rev Med* 2023;74:473-487.

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5. Eapen M, Brazauskas R, Walters MC, et al. Effect of donor type and conditioning regimen intensity on allogeneic transplantation outcomes in patients with sickle cell disease: a retrospective multicentre, cohort study. *Lancet Haematol* 2019;6(11):e585-e596.

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