BRIEF REPORT

Survival of Transplanted Allogeneic Beta Cells with No Immunosuppression

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SUMMARY

The need to suppress a patient's immune system after the transplantation of allogeneic cells is associated with wide-ranging side effects. We report the outcomes of transplantation of genetically modified allogeneic donor islet cells into a man with long-standing type 1 diabetes. We used clustered regularly interspaced short palindromic repeats (CRISPR)–CRISPR-associated protein 12b (Cas12b) editing and lentiviral transduction to genetically edit the cells to avoid rejection; the cells were then transplanted into the participant's forearm muscle. He did not receive any immunosuppressive drugs and, at 12 weeks after transplantation, showed no immune response against the gene-edited cells. C-peptide measurements showed stable and glucose-responsive insulin secretion. A total of four adverse events occurred, none of which were serious or related to the study drug. (Funded by the Leona M. and Harry B. Helmsley Charitable Trust; EudraCT number, 2023-507988-19-00; ClinicalTrials.gov number, NCT06239636.)

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The discovery and clinical adoption of the calcineurin inhibitor cyclosporin A was a major milestone for the transplantation field and allowed the successful routine transplantation of allogeneic organs. However, the toxicity of immunosuppression leads to considerable morbidity and mortality among patients receiving transplants.

Exogenous insulin has been used in the treatment of type 1 diabetes mellitus for more than 100 years. Intensive insulin therapy delays the onset and slows the progression of long-term complications[1] and improves life expectancy.[2] However, insulin remains a treatment and is not a cure; persons with early-onset type 1 diabetes continue to have a reduced quality of life, an elevated risk of serious cardiovascular outcomes, and a shortened life span.[3]

We have shown previously that transplantation of islet cells obtained from a deceased human donor or from a rhesus monkey and edited to be hypoimmune cured diabetes in allogeneic, diabetic, humanized mice[4] and in an allogeneic, diabetic cynomolgus monkey, respectively, without the use of immunosuppression. Here, we report the results of a proof-of-concept study of the transplantation of gene-edited, hypoimmune platform (HIP) islet cells in a patient with long-term type 1 diabetes, without the use of immunosuppression. The depletion of HLA class I and II protects against adaptive T-cell rejection but renders the engineered cells susceptible to innate immune-cell killing through a mechanism known as missing-self recognition. Overexpression of CD47 inhibits such innate killing through

the inhibition of macrophages and natural killer cells. The study was an investigator-initiated, first-in-human, open-label study of UP421, a therapeutic product composed of gene-edited human HIP islet cells that has been approved by the Swedish Medical Products Agency and the Swedish Ethical Review Authority (see the Supplementary Appendix, which, along with the protocol, is available with the full text of this article at NEJM.org).

CASE REPORT

A 42-year-old man with a 37-year history of type 1 diabetes provided written informed consent to participate in the study. He fulfilled eligibility criteria. No additional patients were enrolled in this study. The participant had a glycated hemoglobin level of 10.9% (96 mmol per mole), undetectable endogenous insulin production (i.e., no measurable C-peptide), and detectable glutamic acid decarboxylase and islet antigen 2 autoantibodies (indicators of an autoimmune cause of his disease) and was receiving a daily insulin dose of 32 units.

A blood type O–matched pancreas from a 60-year-old donor with a glycated hemoglobin level of 6.0% (42 mmol per mole) became available, and islets were isolated after 5 hours 11 minutes of cold ischemia at Uppsala University Hospital. These islets had a glucose-stimulated insulin secretion index of 16.7 and a purity of 87%. The islets were shipped to Oslo University Hospital for gene editing. At the manufacturing facility of the hospital, the islets were dissociated into single cells, and the genes *B2M* (encoding a component of class I HLA) and *CIITA* (encoding a master regulator of class II HLA transcription) were inactivated with the use of the nuclease Cas12b (clustered regularly interspaced short palindromic repeats [CRISPR]–CRISPR-associated protein 12b) and guide RNAs. The cells were then allowed to recluster and rest before they were again dissociated and transduced with a lentiviral vector containing *CD47* complementary DNA. Of the edited islet cells, 85.8% were negative for HLA class I, 100% were negative for HLA class II, and 46.4% had high CD47 expression (Fig. 1A). The final cellular product (UP421) thus contained fully edited HLA-depleted HIP islet cells with high CD47 expression, some HLA class I and II double-knockout cells with endogenous CD47 levels, and islet cells with retained HLA expression (wild type) and varying CD47 levels (Fig. 1B). Gene editing did not change the composition of the islets. Approximately 66% of the islet cells in the study were beta cells (Fig. 1C).

The engineered islet cells were then shipped to Uppsala University Hospital for implantation. With the participant under general anesthesia, a small (3.8 cm) skin incision was made over the participant's left brachioradialis muscle (Fig. 1D). A total of 79.6 million engineered HIP islet cells were prepared into 17 syringes and delivered through 17 injections into the muscle. In each injection, the islets were distributed in a linear pearl-on-string pattern while the syringe was slowly pulled back. The participant remained hospitalized overnight to monitor for immediate complications and was discharged the following day. The participant did not receive any glucocorticoids or antiinflammatory or immunosuppressive medications.

We monitored the participant's immune response against each of the islet-cell subpopulations over 12 weeks. The wild-type islet cells remaining in the graft induced strong T-cell activation and killing, which peaked on day 7 (Fig. 2A and 2B) but were spared by innate immune cells (natural killer cells and macrophages) (Fig. 2C and 2D). The wild-type islet cells induced an immediate IgM response (evident at day 7), and a subsequent immunoglobulin class switch to IgG occurred between days 14 and 21 (Fig. 2E). Cell killing mediated by complement-dependent and antibody-dependent cellular cytotoxicity was observed at each time point after the transplantation (Fig. 2F and 2G). The wild-type islet cells were killed when incubated with the participant's peripheral-blood mononuclear cells (PBMCs) combined with his serum containing antibodies and complement to simulate his comprehensive immune response (Fig. 2H). The double-knockout islet cells remaining in the graft induced a strong innate immune response and were killed by the participant's innate natural killer cells and macrophages (both cell types can sense HLA deficiency[6]) and by the participant's PBMCs and serum (Fig. 2C, 2D, and 2H). In spite of the ongoing immune responses against wild-type and double-knockout cells, HIP islet cells were not killed by the participant's immune cells, did not induce antibodies, and survived when incubated

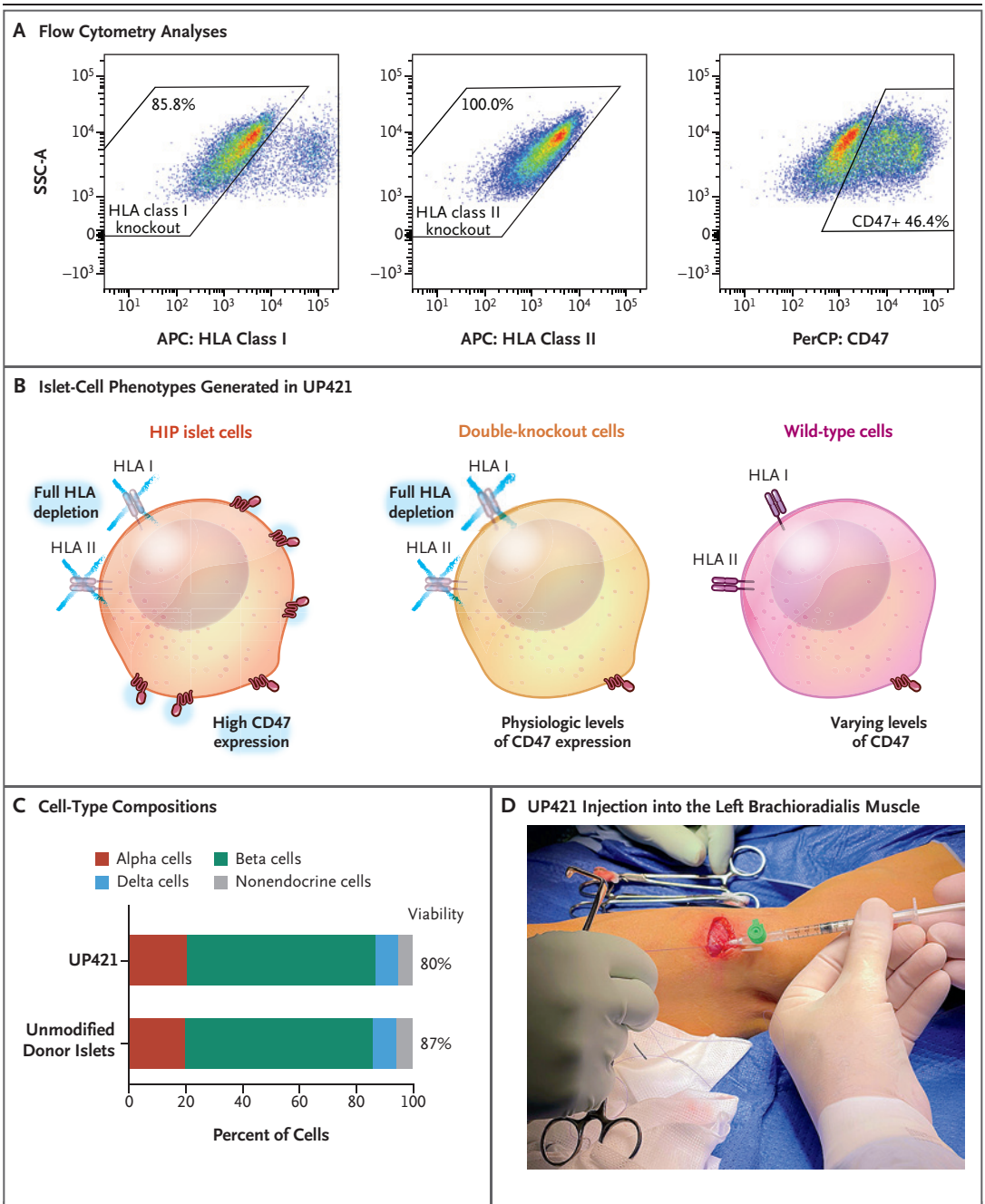

Figure 1. Characterization and Transplantation of the Engineered Allogeneic Islet-Cell Product UP421.

Panel A shows the results of the flow cytometry analyses of the final gene-edited islet-cell product (UP421) for the surface expression of HLA class I, HLA class II, and CD47, with the percentages for HLA class I and II depletion and CD47 overexpression. Panel B shows the three islet-cell phenotypes that were generated in the UP421 product. The hypoimmune platform (HIP) islet cells showed both full HLA depletion and CD47 overexpression, whereas HLA class I– and class II–depleted double-knockout islet cells showed physiologic CD47 expression. Wild-type islet cells retained physiologic HLA expression and showed varying levels of CD47 expression. Panel C shows the cell-type compositions of the unmodified donor islets and the final UP421 cell product. Gene editing did not change the cell makeup of the islets. Panel D shows 1 of the 17 injections into the left brachioradialis muscle in the participant. APC denotes allophycocyanin, PerCP peridinin–chlorophyll–protein, and SSC-A side scatter area.

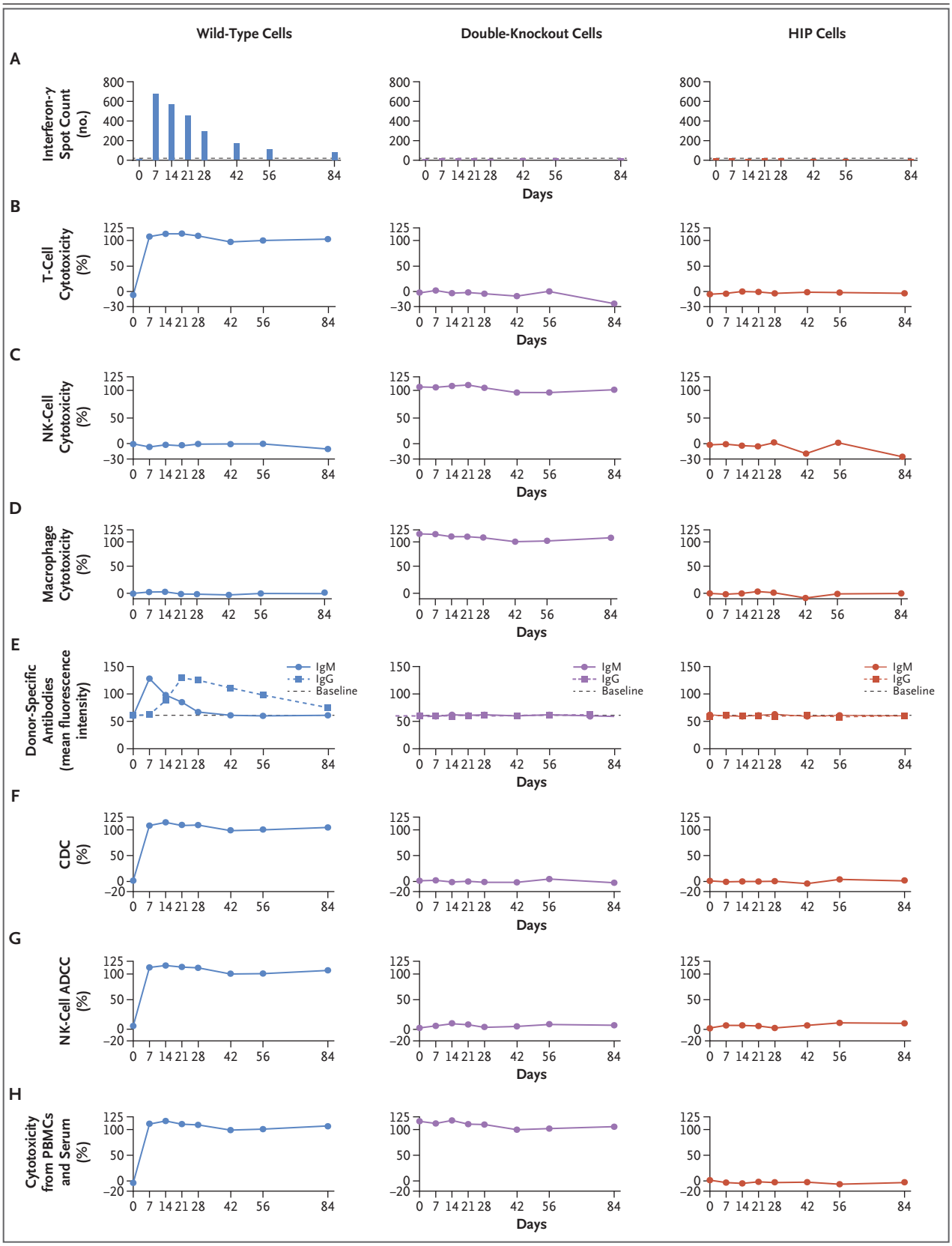
Wild-Type Cells
Double-Knockout Cells
HIP Cells
A
Interferon-γ Spot Count (no.)
B
T-Cell Cytotoxicity (%)
C
NK-Cell Cytotoxicity (%)
D
Macrophage Cytotoxicity (%)
E
Donor-Specific Antibodies (mean fluorescence intensity)
IgM
IgG
Baseline
F
CDC (%)
G
NK-Cell ADCC (%)
H
Cytotoxicity from PBMCs and Serum (%)
Days

Figure 2 (facing page). Cellular and Humoral Immune Components in the Participant over 12 Weeks.

Panel A shows interferon-γ enzyme-linked immunosorbent spot (ELISpot) data from the assessment of the participant's T-cell activation on restimulation with one of the three islet-cell subpopulations. Strong T-cell activation that peaked at approximately 7 days was seen only against wild-type cells. Panel B shows the results of corresponding T-cell cytotoxicity assays. The participant's T cells only killed wild-type cells. Panels C and D show the results of innate immune-cell killing assays with natural killer (NK) effector cells and macrophages, respectively. Only double-knockout cells were killed. Panel E shows mean fluorescence intensity of antibody binding against the UP421 wild-type cell, double-knockout cell, or HIP cell subpopulations. Antibodies were only generated against wild-type cells, with IgM antibody binding peaking early (circles with solid line), followed by a class switch to IgG antibodies (squares with dashed line). No antibodies against double-knockout or HIP islet cells were generated (the dashed lines show the background staining). Panels F and G show antibody-mediated complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) with NK effector cells, respectively. Only wild-type islet cells, against which antibodies were measurable, were killed in these assays. Panel H shows the participant's comprehensive immune response orchestrated by peripheral-blood mononuclear cells (PBMCs) and serum containing antibodies and complement. In this assay, both the wild-type islet cells and the double-knockout cells were killed, but the HIP islet cells survived because they escape all the immune components in the participant.

with the participant's PBMCs and serum (Fig. 2A through 2H). Thus, we did not detect any immune response targeting the HIP islet cells over the course of the study.

We assessed allograft function in the participant by means of serial high-sensitivity C-peptide measurements and observed that the levels were stable between 7 days and 12 weeks (Fig. 3A). At screening, the participant had no detectable C-peptide levels during a mixed-meal tolerance test, but at 4, 8, and 12 weeks, C-peptide levels increased in response to a liquid meal beverage containing fats, protein, and carbohydrates (Fig. 3B). The participant's exogenous insulin dose (in terms of both total dose and dose per kilogram of body weight) was increased after islet transplantation to prevent hyperglycemic spikes that could have harmed the fresh islet graft (Fig. 3C and 3D). His glycated hemoglobin level decreased by approximately 42% over the 12-week follow-up period (Fig. 3E), probably entirely in response to exogenous insulin. Persistence of the islet allograft was confirmed by magnetic resonance imaging (MRI) at 4 and 8 weeks. The MRI findings showed several punctate signals at each injection site and no inflammation or evidence of pathologic changes (Fig. S1A in the Supplementary Appendix). Positron-emission tomography and MRI (PET-MRI) at 12 weeks showed specific sites of high radiotracer uptake in the areas of the islet allografts, which could be delineated from surrounding muscle (Fig. S1B). The use of a glucagon-like peptide 1 receptor (GLP-1R)–targeting PET tracer has been shown to permit the visualization of functional pancreatic islet grafts, which express high levels GLP-1R, in the brachioradialis muscle.[7] Standardized uptake value plots support tracer accumulation in the graft areas and washout in the adjacent muscle tissue (Fig. S1C).

After 12 weeks, the participant continues to do well. A total of four adverse events occurred, none of which were serious. Mild thrombophlebitis developed in the participant at the site of the peripheral intravenous catheter, and he had paresthesia in his left lower arm, which was possibly related to the surgical procedure (see the Supplementary Appendix).

DISCUSSION

The results of this first-in-human study are consistent with immune evasion by allogeneic, hypoimmune-engineered islet cells. These cells, transplanted and engrafted in the forearm muscle of a person with type 1 diabetes, did not induce an immune response and escaped the alloimmune responses induced against nonedited or partially edited cells. The results are also consistent with stable beta-cell function over a 12-week period. Our findings are encouraging in consideration of the reported association between early graft function and long-term clinical outcomes.[8] Although T-cell–mediated immunity and donor-specific antibody surges peaked during the first 3 weeks, the HIP islet cells did not induce a measurable immune-cell or antibody-mediated response throughout the 12-week follow-up period. The absence of an alloimmune response against the HIP islet cells is consistent with our earlier findings in a diabetic cynomolgus monkey that received allogeneic hypoimmune-engineered islet allografts.[5] C-peptide levels in the monkey were stable throughout the 6-month follow-up period.

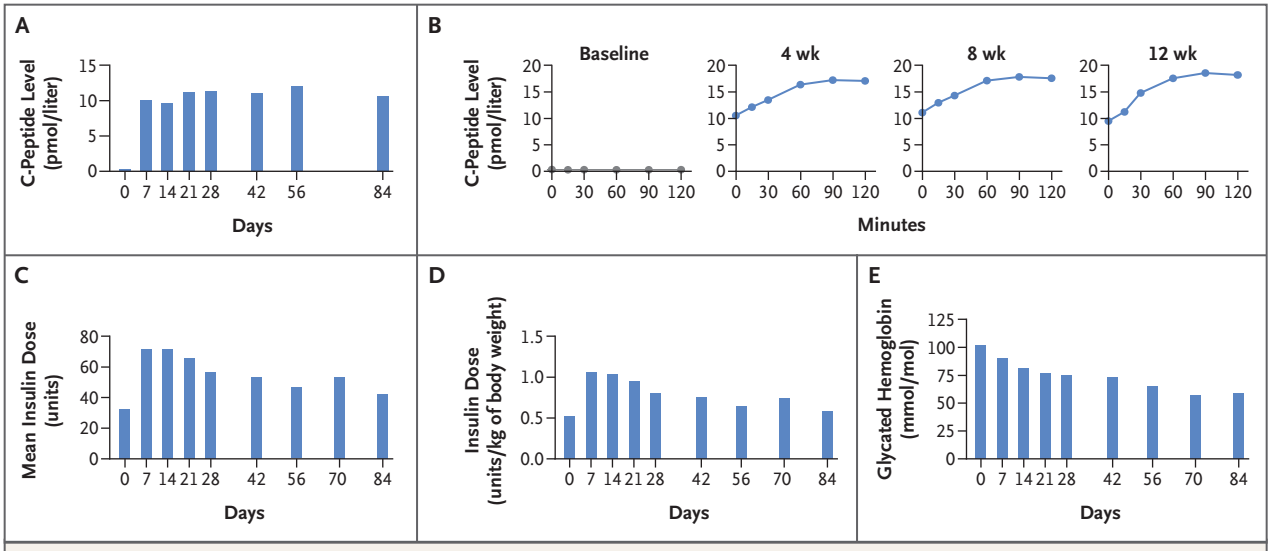

Figure 3. Postoperative Persistence and Function of HIP Islet-Cell Allografts.

Panel A shows that the participant did not have measurable C-peptide levels before receiving the UP421 islet-cell product. C-peptide levels were measured over the 12-week follow-up period with a high-sensitivity assay, which showed that the levels remained stable near or above 10 pmol per liter. Panel B shows that the participant did not have any C-peptide response to a mixed-meal tolerance test before transplantation, but at 4, 8, and 12 weeks after transplantation, an increase in the C-peptide level was observed, a finding suggestive of functional beta-cell grafts. Panels C and D show the mean insulin doses (the total dose and the dose per kilogram of body weight, respectively) that were administered during the study period. Panel E shows glycated hemoglobin levels over the 12-week follow-up period.

Moreover, a previous study in humanized mouse models of diabetes showed that hypoimmune islets escape the etiologic autoimmune response.[4]

The gene-editing process did not change the cell-type composition of the islets, a finding that is in keeping with the results of preclinical studies showing that gene editing and lentiviral transduction does not affect islet composition or insulin secretion.[4,5] Thus, CD47 overexpression does not seem to negatively affect insulin secretion, although it was recently suggested that genetic ablation of CD47 stimulates exocytosis of granules containing insulin.[9] The dose of 79.6 million HIP islet cells was intentionally low to meet the regulatory requirements for a first-in-human study. It seems unlikely that the small dose favorably affected cell survival, since we observed a strong immune reaction against the unmodified and partially edited islet cells. Moreover, a smaller total islet mass has not been associated with graft survival in allogeneic islet transplantation.[10] A mean (±SD) of 11,547±1604 islet equivalents per kilogram of body weight,[11] with 1560 cells per islet equivalent,[12] is capable of producing sustained insulin independence; the dose of 79.6 million HIP islet cells used in the current study was 7.1% of that dose. The observed C-peptide levels were consistent with the transplanted HIP islet-cell mass, which suggests that a full dose of HIP islet cells (i.e., approximately 18 million per kilogram) could produce insulin independence. The fact that the HIP islet-cell graft could be clearly identified on PET-MRI indicates radiotracer uptake and therefore vascularization in the forearm muscle, a finding that is similar to our previous observations with non–genetically modified islets.[13] Furthermore, the survival of allogeneic HIP islet-cell grafts for 6 months in nonhuman primate quadriceps muscle without evidence of a reduction in mass[14] or weakening of endocrine function[5] is consistent with muscle being a viable site for islet engraftment. The stability of the C-peptide levels over time in the participant in the current study also supports this hypothesis.

In most studies of allogeneic islet transplantation, patients with type 1 diabetes have received more than one islet transplant. Across different studies, patients have received a median of two islet transplants; some have received three[15] or five[10,15] allogeneic islet transplantations. HIP islet-cell grafts could, in the future, be transplanted

iteratively to adjust for insulin independence. The HLA-replete cell population in the UP421 product could theoretically induce donor-specific antibodies and leave the patient sensitized, because a single sensitization event by an allogeneic HLA can result in lifelong B-cell memory with a risk of reactivation after subsequent exposure. However, anti-HLA donor-specific antibodies do not pose a risk for subsequent HIP islet-cell transplants, and the rapid disappearance of the unmodified cells may result in a weaker antibody response or a reduced odds of such occurrence. The induction of donor-specific HLA antibodies after allogeneic islet-cell transplantation has been reported,[15] but this often occurred several months after transplantation.[16] Most patients do not have development of donor-specific antibodies even after receiving multiple islet transplants.[16]

The risks of gene editing in cellular therapeutics have been investigated most comprehensively in chimeric antigen receptor (CAR) T cells. In a recent safety analysis involving 783 patients from 38 trials of T-cell therapy with more than 2200 total patient-years of observation, only a single case of secondary T-cell lymphoma was reported.[17] There was no evidence of CAR transgene integration in lymphoma tissue and no indication that insertional mutagenesis contributed to T-cell transformation, although an isolated case of indolent CAR-positive T-cell lymphoma that occurred after CAR T-cell therapy had been reported previously.[18] Although integration of viral vectors into specific genes has been reported to cause notable clonal expansions in engineered T cells,[19,20] in neither case were those malignant. With the established safety of CAR T-cell therapy, the risk for insertional mutagenesis in engineered islet products could be lower, given that islet cells are generally nonproliferative. The availability of the CD47-targeting antibody magrolimab, which was shown to selectively and effectively eliminate HIP islet cells in allogeneic, diabetic humanized mice,[4] could add another layer of safety for clinical HIP islet-cell transplantation.

On the basis of previous preclinical studies, the hypoimmune phenotype provides protection against alloimmunity for cell types other than islet cells.[21-23] Although inducing immune tolerance of allogeneic transplants has long been viewed as a holy grail, our study, although preliminary, suggests that immune evasion is an alternative concept for the circumvention of allorejection.[24]

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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