CORRESPONDENCE

Long-Term Survival of Hypoimmune Allogeneic Islets without Immunosuppression

TO THE EDITOR: For patients with type 1 diabetes, transplantation of allogeneic islet cells (obtained from deceased human donors or stem-cell sources) that are capable of survival without immunosuppression have the potential to improve the safety profile of β-cell replacement therapy.[1] We previously described 3-month outcomes of intramuscular transplantation of UP421, a therapeutic product consisting of allogeneic HLA class I– and II–depleted, CD47-overexpressing hypoimmune platform (HIP) islet cells, in a participant with long-standing type 1 diabetes.[2] The participant did not receive any immunosuppressive medication. Follow-up for the primary safety end point (treatment-related adverse events within 12 months after transplantation) has now been completed, and the participant has reached the 14-month follow-up evaluation. The protocol and the statistical analysis plan for this study are available with the full text of this letter at NEJM.org.

Six adverse events occurred, of which two (mild pharyngitis and a foot ulcer) arose after the 3-month visit (Table S1 in the Supplementary Appendix, available at NEJM.org). Analyses of secondary end points, including persistent graft survival, endocrine function, and immune evasion, showed positive results. Positron-emission tomography (PET) and magnetic resonance imaging showed sustained graft viability, with persistently high radiotracer uptake that was localized to the allograft site at 12 months (Fig. 1A). PET signal quantification at 12 months showed an early peak in tracer uptake, consistent with enhanced vascular integration of the transplanted islets (Fig. 1B). Circulating C-peptide levels (a measure of β-cell function) remained detectable throughout, consistent with ongoing allograft function.

After stable glycemic control through the 3-month visit, the participant became less adherent to his insulin-management protocol and administered fewer exogenous insulin doses than recommended. He had an increase in the glycated hemoglobin level at the 6-month visit as compared with the 3-month visit (Fig. 1C) and an increase in the glucose management indicator[3] at the 9-month visit as compared with the two previous visits (Fig. 1D), as well as transiently lower levels of C-peptide at 9 months and at 12 months than at earlier time points (Fig. 1D). To distinguish irreversible graft attrition from reversible hyperglycemia-induced β-cell exhaustion,[4] intensified glycemic monitoring was implemented to test whether C-peptide levels would recover with improved glycemic control. At the 14-month visit, the glycated hemoglobin level and glucose management indicator had improved, and both the fasting C-peptide levels (Fig. 1C) and the responses during mixed-meal tolerance testing (Fig. S1) had returned to levels similar to those at 6 months. These findings confirm stable function of the allograft beyond 1 year.

Immune analyses were performed with the participant's peripheral-blood mononuclear cells and serum against donor HIP cells (modified splenocytes from the same donor from which HIP islets were derived), HLA class I and II double-knockout splenocytes, and unedited wild-type splenocytes. The results of these analyses, together with previously reported immune data obtained with the use of HIP, double-knockout, and wild-type islet subpopulations, are provided in Figure S2. In a finding consistent with the results obtained from in vitro assays at 3 months, no cellular or humoral immune responses against the HIP cells were detected up to 1 year after transplantation (Fig. S3). Specifically, no donor-specific IgG antibodies against HIP cells were detected throughout the study by flow cytometry with the use of an assay capable of identifying both HLA-targeting and non–HLA-targeting antibodies.

Islet-specific autoantibody levels remained unchanged, with persistently elevated levels of an-

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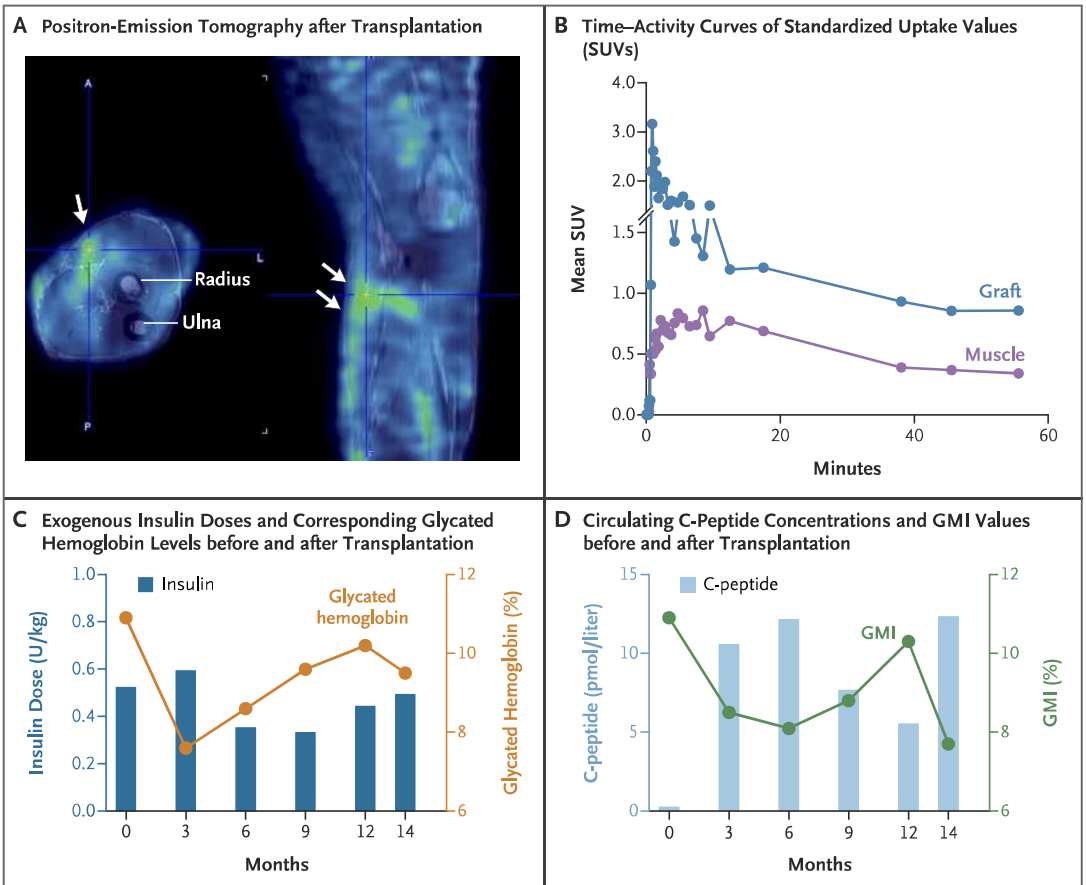


Figure 1. Persistent Engraftment and Function of the Islet Allograft.

Panel A shows positron-emission tomographic images obtained with the use of the glucagon-like peptide-1 receptor (GLP-1R)–targeting radiotracer [^{68}Ga]Ga-NODAGA-exendin-4 at 12 months after transplantation of UP421 (gene-edited islet cells). The GLP-1R signal localizes to the sites of intramuscular injection of UP421 (arrows) and is similar in intensity and distribution to that observed at 12 weeks. Panel B displays the time–activity curves of standardized uptake values (SUVs) at the graft sites as compared with adjacent muscle. Tracer accumulation was confined to the graft sites and showed an early, marked peak in intensity, consistent with vascular integration of the transplanted islets. Panel C shows exogenous insulin doses and corresponding glycated hemoglobin levels before and after transplantation. A reduction in the insulin dose at 6 months after transplantation was accompanied by an increase in the glycated hemoglobin level, which subsequently decreased with the resumption of higher insulin doses at 14 months. Panel D shows circulating C-peptide concentrations before and after transplantation and corresponding glucose management indicator (GMI) values (with each GMI calculated on the basis of the average glucose level over a period of 14 days). C-peptide was undetectable before UP421 infusion and remained detectable throughout follow-up. Transient increases in the GMI were associated with reversible suppression of C-peptide levels. Graft function remained stable when the GMI was below 8.5%.

tibodies against glutamic acid decarboxylase 65 (GAD65) and very low levels of antibodies against islet antigen 2 (IA-2). Antibodies against zinc transporter 8 (ZnT8) were not detected. As for the responses to unmodified splenocytes, T-cell reactivity declined, and assays for complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity were positive. Although antibodies can effectively mediate cytotoxicity even at very low concentrations, no antibody activity directed against HIP cells was observed in this participant. The survival and function of the HIP islet allograft and the durable absence of alloreactivity against HIP cells show that HIP engineering provided immune protection through 14 months of follow-up.

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Per-Ola Carlsson, M.D., Ph.D.,[1] Xiaomeng Hu, Ph.D.,[1] Hanne Scholz, Ph.D.,[2] Torbjörn Lundgren, M.D., Ph.D.,[3] Sofie Ingvast, B.Sc.,[1] Tim Scholz, M.D., Ph.D.,[1] Olof Eriksson, Ph.D.,[1] Per Liss, M.D., Ph.D.,[1] Irina Velikyan, Ph.D.,[1] Di Yu, Ph.D.,[1] Grigol Tediashvili, B.Sc.,[4] Tobias Deuse, M.D.,[4] Olle Korsgren, M.D., Ph.D.,[1] and Sonja Schrepfer, M.D., Ph.D.[1]

[1] Uppsala University, Uppsala, Sweden; [2] Oslo University Hospital, Oslo; [3] Karolinska Institute, Stockholm; [4] University of California, San Francisco, San Francisco.

Per-Ola Carlsson can be contacted at per-ola.carlsson@mcb.uu.se.

Xiaomeng Hu and Hanne Scholz contributed equally to this letter.

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