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# Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation in New-Onset Type 1 Diabetes: A Multicenter Analysis



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**Type 1 diabetes (T1D) is one of the major autoimmune diseases affecting children and young adults worldwide. To date, the different immunotherapies tested have achieved insulin independence in <5% of treated individuals. Recently, a novel hematopoietic stem cell (HSC)-based strategy has been tested in individuals with new-onset T1D. The aim of this study was to determine the effects of autologous nonmyeloablative HSC transplantation in 65 individuals with new-onset T1D who were enrolled in two Chinese centers and one Polish center, pooled, and followed up for 48 months. A total of 59% of individuals with T1D achieved insulin independence within the first 6 months after receiving conditioning immunosuppression therapy (with antithymocyte globulin and cyclophosphamide) and a single infusion of autologous HSCs, and 32% remained insulin independent at the last time point of their follow-up. All treated subjects showed a decrease in HbA<sub>1c</sub> levels and an increase in C-peptide levels compared with pretreatment. Despite a complete immune system recovery (i.e., leukocyte count) after treatment, 52% of treated individuals experienced adverse effects. Our study suggests the following: 1) that remission of T1D is possible by combining HSC transplantation and immunosuppression; 2) that**

**autologous nonmyeloablative HSC transplantation represents an effective treatment for selected individuals with T1D; and 3) that safer HSC-based therapeutic options are required.**

The incidence of type 1 diabetes (T1D) has been significantly increasing worldwide in the last decade, thus becoming the most common autoimmune disorder in children (1). T1D is characterized by a selective and aggressive destruction of insulin-producing  $\beta$ -cells orchestrated by autoreactive T cells (2,3). Unfortunately, exogenous insulin therapy does not always achieve the necessary metabolic control (4), nor does it prevent the occurrence of disease-associated degenerative macrovascular and microvascular complications (5) or halt  $\beta$ -cell decline (6).

The concept of the use of immunotherapeutic strategy to cure T1D has emerged from hallmark data generated using the NOD mouse model and has allowed for a better understanding of the pathogenesis of T1D (7). Several clinical trials—designed based on the preclinical successful targeting of components of innate and adaptive immune responses—performed thus far have failed to cure

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T1D (3,8); only in the anti-CD3 monoclonal antibody (mAb) trial (using teplizumab in the Protégé Study) did 5% of individuals become insulin independent (9). In this daunting scenario, a trial conducted by Voltarelli et al. (10) succeeded in exploiting hematopoietic stem cells (HSCs) to treat new-onset T1D and achieved encouraging results, paving the way for another three trials, which were initiated worldwide (11,12). The rationale for the use of HSCs in treating subjects with T1D is based upon the immunoregulatory properties of HSCs, which may help to rescue peripheral tolerance toward pancreatic  $\beta$ -cells by reshaping the immune response (13,14).

Our aim is to provide updated results on the worldwide use of autologous HSC transplantation (AHST) in T1D patients, to evaluate potential adverse events, and to explore the successes and potential pitfalls of this novel therapy.

## RESEARCH DESIGN AND METHODS

### Patient Characteristics

Sixty-five individuals were enrolled in three independent clinical trials. In the “Polish protocol” (conducted in the Department of Hematology, Oncology and Internal Diseases, Medical University of Warsaw;  $n = 24$ ), the inclusion criteria were as follows: individuals of both sexes, 12–35 years of age, who had received a diagnosis of T1D during the previous 6 weeks that had been confirmed by the measurement of serum levels of anti-GAD antibodies and the absence of diabetic ketoacidosis (DKA). Study enrollment began in March 2008.

In the two trials conducted in the Chinese population (conducted in the Division of Endocrinology, The Affiliated Drum Tower Hospital of Nanjing and the Shanghai Jiao Tong University School of Medicine;  $n = 13$  and 28, respectively), the inclusion criteria were as follows: individuals of both sexes, 12–35 years of age, who had received a diagnosis of T1D during the previous 12 months, the presence of a high-risk allele for T1D (e.g., HLA-DQB1), and positivity for at least one autoantibody against  $\beta$ -cell antigens (e.g., GAD, insulinoma-2-associated autoantibodies, islet cell antibodies) even in the presence of DKA. Study enrollment began in July 2008. Baseline glycometabolic and clinical parameters were similar in all trials (Table 1). Individuals were all receiving insulin-intensive treatment.

### Treatment

All individuals received the following treatment (Supplementary Table 1): 1) HSC mobilization initiated using cyclophosphamide, administered in two doses ( $2 \text{ g/m}^2$ ) with an interval of 12 h, and granulocyte colony-stimulating factor (G-CSF) ( $5\text{--}10 \text{ }\mu\text{g/kg}$ ) daily beginning the day after cyclophosphamide administration (leukapheresis was initiated when the  $\text{CD34}^+$  cell count in peripheral blood was  $>10$  leukocytes/ $\mu\text{L}$ ), and collected cells were frozen; 2) a conditioning regimen was initiated using cyclophosphamide ( $200 \text{ mg/kg}$  over 4 days) and thymoglobulin ( $2.7 \pm 2.4 \text{ mg/kg}$  over 5 days) before transplantation; 3) HSCs were administered at a mean dose of  $5.8 \pm 0.8 \times 10^6/\text{kg}$

**Table 1—Baseline demographic, immunological, and clinical characteristics of T1D individuals treated with nonmyeloablative AHST**

Characteristics	Values
Total patients included	65
Age (years)	$20.4 \pm 5.5$
Sex	
Male	41
Female	24
BMI ( $\text{kg/m}^2$ )	$18.1 \pm 3.1$
HbA <sub>1c</sub> (mmol/mol)	$88.7 \pm 4.7$
C-peptide (ng/mL)	$0.69 \pm 0.04$
Autoantibodies	
GAD	52
GAD/ICA	4
GAD/IA2A	3
IAA	4
ICA	2
DKA or DK history	
No DKA/DK	43
DKA	21
DK	1
HLA-DQB1 allele	
201	17
303	8
503	8
302	7
501	5
301	4
601	2
602	2
401	1
604	1
309	1
202	1
331	1
402	1
609	1
603	1
304	1

Data are  $n$  or mean  $\pm$  SD. DK, diabetic ketoacidosis; IA2A, insulinoma-2-associated autoantibodies; IAA, insulin autoantibodies; ICA, islet cell cytoplasmic autoantibodies.

cryopreserved  $\text{CD34}^+$  cells as a single infusion at day 0; and 4) G-CSF was administered at day +1 after transplantation at a dose of  $5 \text{ }\mu\text{g/kg}$  until the neutrophil count in the peripheral blood was  $>1,000$  neutrophils/ $\mu\text{L}$ .

The Polish protocol, however, added two to three plasmapheresis sessions before transplantation to remove autoantibodies and immune complexes. Other associated treatments included infection prophylaxis (with fluconazole and co-trimoxazole for up to 60 days, and acyclovir for up to 35 days after transplantation) and oral antidiabetes drugs (acarbose,  $100 \text{ mg}$  3 times daily over time) in the Polish protocol. Fluconazole, acyclovir, and levofloxacin were administered in the Chinese trials as prophylaxis for infections. Treated individuals were followed up for 48 months.

**Statistical Analysis**

Data are presented as the mean (SE). The statistical significance of differences was tested with a two-tailed paired *t* test and the  $\chi^2$  test. Disease-free survival, defined as requiring no insulin treatment, was analyzed using the actuarial method (15). Further statistical methods are described in the Supplementary Data.

**RESULTS**

**Glycometabolic Control**

Insulin independence was achieved in 59% of individuals within the first 6 months after treatment, and 32% of them were insulin independent at the last time point of their follow-up (Fig. 1A and Supplementary Fig. 1). The probability of disease-free survival, defined as requiring no insulin treatment, was 50% at 12 months after treatment and reached 71% at 48 months (Fig. 1B). The median duration of insulin independence was 12 months (range 12–40 months) (Fig. 1C). The exogenous insulin requirement significantly decreased during the follow-up period, with some individuals still requiring insulin treatment

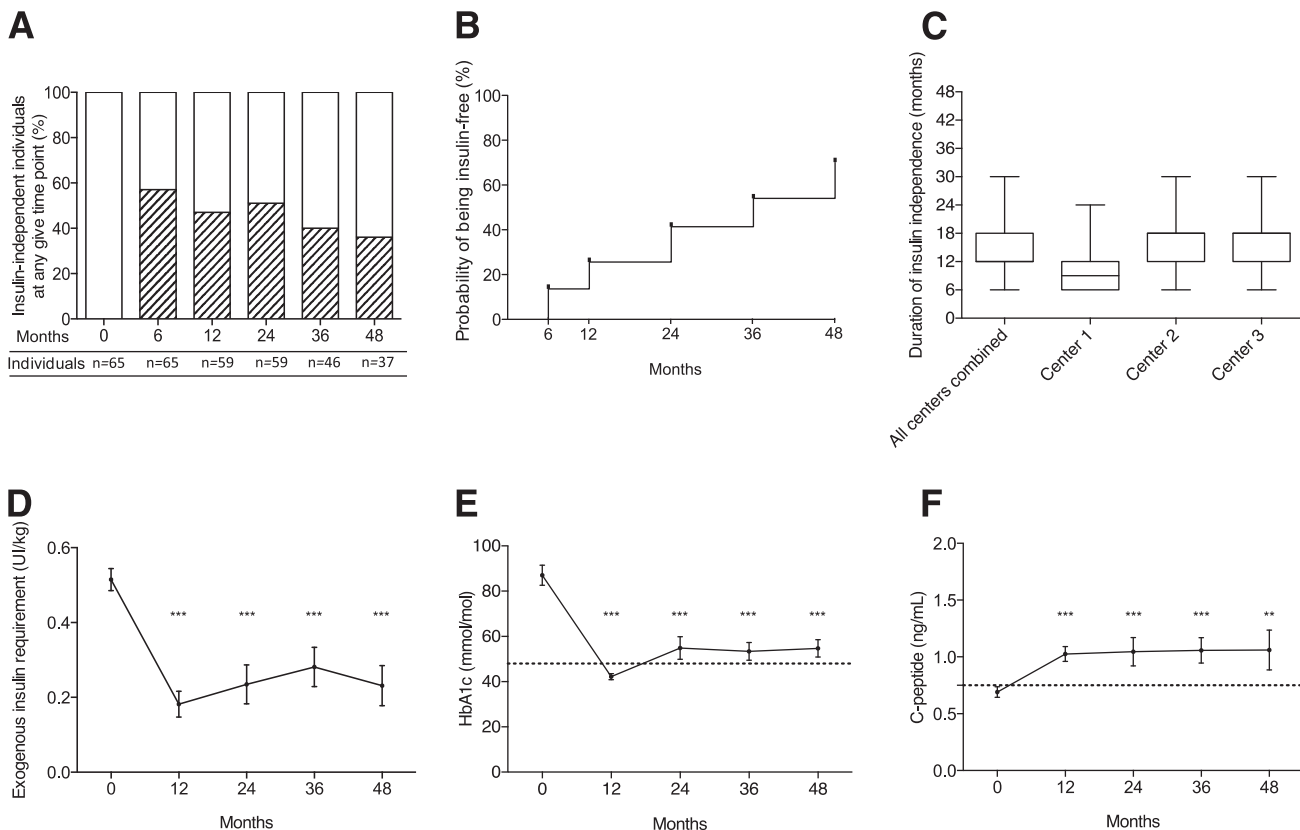
but at a low dosage (<10 units/day) (Fig. 1D). An amelioration of glycometabolic function was confirmed by a significant reduction (50%) of glycated hemoglobin (HbA<sub>1c</sub>) levels after treatment compared with baseline (87.2 ± 4.8 mmol/mol), achieving mean values of 42.6 ± 4.7 and 42.2 ± 1.3 mmol/mol, respectively, at 6 and 12 months of follow-up (*P* < 0.0001), which are similar to those values reported for normoglycemic subjects (HbA<sub>1c</sub> range 20–42 mmol/mol) (Fig. 1E).

**β-Cell Function**

All individuals showed an improvement in β-cell function, as revealed by an increase in C-peptide levels at 6 months after treatment compared with baseline (1.22 ± 0.10 vs. 0.54 ± 0.06 ng/mL, *P* < 0.0001) and over time. In particular, C-peptide levels reached a persistent median value >1.15 ng/mL at 24 months of follow-up that lasted until 48 months after treatment (Fig. 1F).

**Immunological Recovery**

Analysis of leukocyte and neutrophil counts in peripheral blood obtained before and after treatment showed



**Figure 1**—Individuals with T1D treated with nonmyeloablative AHSCT achieved insulin independence, improved glycometabolic control, and maintained pancreatic β-cell function. **A:** Bar graphs depicting percentages of T1D-treated individuals achieving insulin independence during follow-up. **B:** Actuarial curve of the probability of treated T1D individuals without the requirement for exogenous insulin treatment. **C:** Box plots representing the duration of insulin independence (months) in all trials combined and in each single trial. **D–F:** Line graph showing exogenous insulin requirement, HbA<sub>1c</sub> levels, and C-peptide levels during follow-up. All data are expressed as the mean ± SEM. Dotted line represents the corresponding value in healthy subjects. All parameters examined were statistically significantly different when comparing baseline values vs. those at 12, 24, 36, and 48 months. \*\**P* < 0.001; \*\*\**P* < 0.0001. UI, units of insulin.

a decrease in leukocytes at 12 months after treatment and a small increase in neutrophils at 6 months, with an overall stabilization of the immune system for the remaining follow-up period (Supplementary Fig. 2A and B).

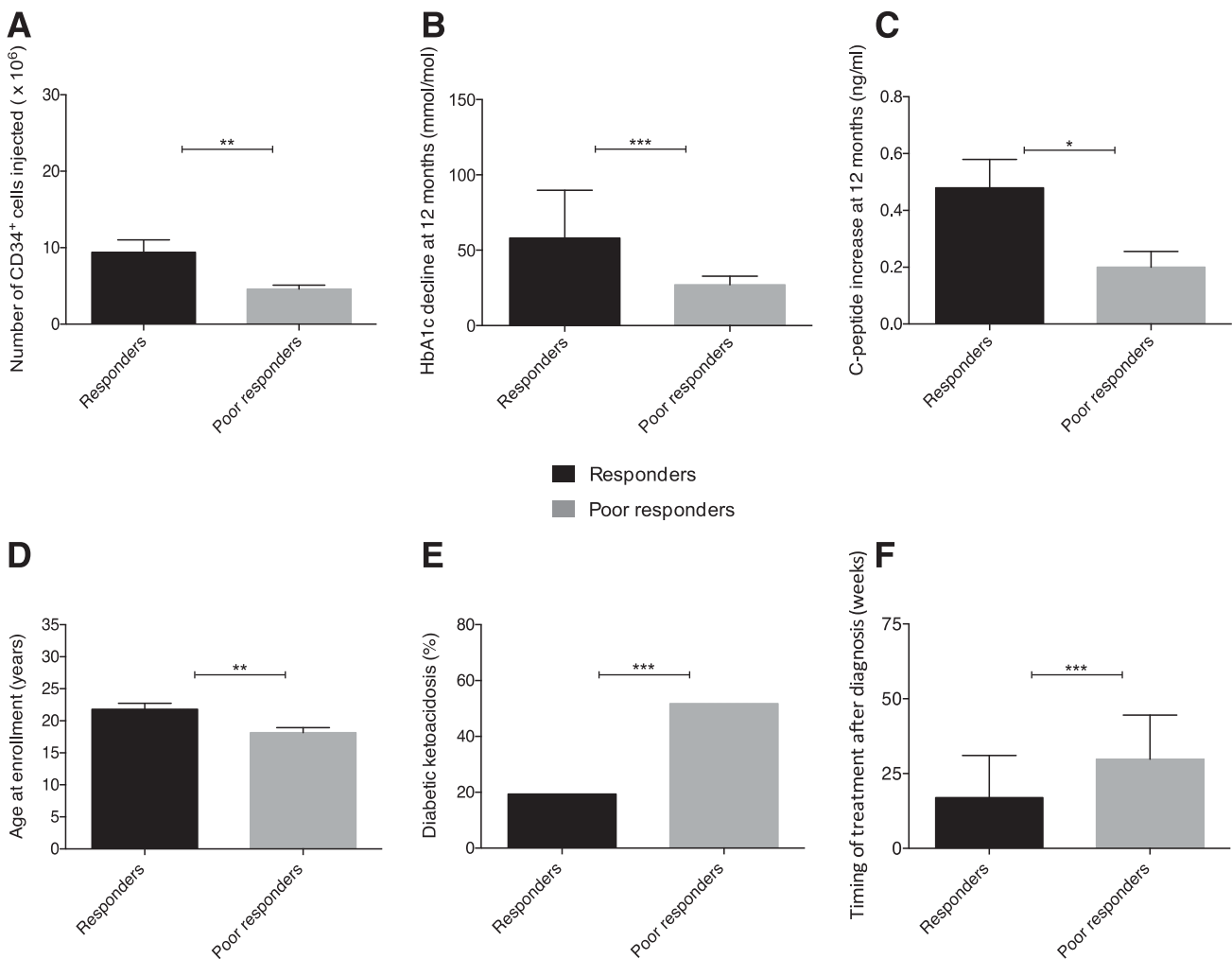
### Correlation Between Treatment and T1D

No significant correlation was found between the number of CD34<sup>+</sup> cells infused and HbA<sub>1c</sub> or C-peptide levels at 12 months. Multivariate analysis was negative for sex, age, and baseline HbA<sub>1c</sub> and C-peptide levels. Interestingly, subjects treated earlier after T1D diagnosis were twice as likely to achieve insulin independence over time than those with a later T1D diagnosis (relative risk = 2.0,  $P = 0.0008$ ). In particular, 82% of individuals treated within 6 weeks from the time of T1D diagnosis became insulin independent compared with 40% of subjects whose

treatment was initiated at a later time point after T1D diagnosis.

### Responders Versus Poor Responders

All individuals receiving AHSCT were grouped according to the insulin treatment required over the follow-up period and compared. Four subjects were lost at follow-up after 6 months of treatment. Thirty-six of 61 subjects achieved insulin independence for at least 6 months and were identified as the responder group. Twenty-five of 61 subjects required insulin treatment for the entire follow-up period, although at lower doses, and constituted the poor responder group. The number of CD34<sup>+</sup> cells injected was significantly lower in poor responders compared with responders ( $P = 0.01$ , Fig. 2A), while no differences were observed with regard to leukocyte count or neutrophil percentage at 12 months after treatment and over time.



**Figure 2**—Responders and poor responders to nonmyeloablative AHSCT. A–C: Bar graphs depicting the number of CD34<sup>+</sup> cells infused, the reduction in HbA<sub>1c</sub> levels from baseline and 12 months after treatment, and the increase in C-peptide levels from baseline and 12 months after treatment in responders vs. poor responders. D–F: Bar graphs depicting the age of individuals at the time of study enrollment, the percentage of subjects who experienced DKA, and the average time of diagnosis of T1D in responders vs. poor responders. All data are expressed as the mean ± SEM. All parameters examined were statistically significantly different when comparing responders vs. poor responders. \* $P < 0.01$ ; \*\* $P < 0.001$ ; \*\*\* $P < 0.0001$ .

HbA<sub>1c</sub> levels significantly decreased in responders at 12 months ( $P < 0.0001$ , Fig. 2B). The increase in C-peptide level at 12 months compared with baseline was more evident in responders ( $P = 0.02$ , Fig. 2C). Poor responders were younger at the time of study enrollment, were treated later after T1D diagnosis, had more instances of DKA, and had higher HbA<sub>1c</sub> levels at the time of study enrollment (Fig. 2D–F).

### Adverse Events

Thirty-four of 65 treated individuals experienced adverse events after treatment. In particular, neutropenic fever represented the most frequent complication occurring in 7 of 65 individuals, followed by alopecia associated with fever and gastrointestinal symptoms (5 of 65 and 3 of 65, respectively) (Table 2). Severe infectious diseases were registered in 3 of 65 individuals, with the death of 1 individual as a result of *Pseudomonas aeruginosa* sepsis. Overall, the bone marrow, gastrointestinal tract, and immune system were the major targets for the occurrence of adverse events. Prophylaxis for infection included the administration of co-trimoxazole in the Polish study and levofloxacin in the two Chinese trials.

### DISCUSSION

AHSCT represents the first approach ever shown to be successful in treating early-onset T1D. Our data confirmed that in a group of 65 individuals who were followed up for 48 months, AHSCT in a nonmyeloablative setting can induce the remission of T1D. Considering that intensive treatment with exogenous insulin only delays the occurrence of T1D complications, more strategies have been explored to improve outcomes of patients with T1D. To date, islet cell transplantation, pancreas transplantation, and anti-CD3 mAb administration have been authorized for clinical use (9,16,17). Although pancreas transplantation achieved insulin independence in 60% of subjects at 4 years after the transplant (with a median graft survival time of 9 years, according to the United Network for Organ Sharing data registry analysis), the surgical procedure is still associated with a substantial mortality rate (78% of individuals survived at 1 year) (18). Conversely, while both islet cell transplantation and treatment with anti-CD3 mAbs are considered relatively safe, they have been shown to achieve insulin independence in only a very few subjects at 5 years of follow-up (25% and 5%, respectively) (9). Despite this, islet cell transplantation has been very successful in halting the progression of both short-term and long-term complications of T1D (19,20). Our analysis demonstrates that AHSCT in individuals with T1D achieved insulin independence in 59% of subjects at 6 months, and it was maintained in 32% of subjects at the last time point of their follow-up.

Moreover, subjects who responded to treatment as not requiring exogenous insulin therapy for at least 6 months after transplantation showed a more significant

**Table 2—Adverse events occurring during the study treatment follow-up**

	<i>n</i>
Neutropenic fever	7
Alopecia, gastric tract symptoms	5
Alopecia, fever	3
Fever, bone marrow suppression	2
Allergic reaction to ATG	2
Patient died due to sepsis and DIC	1
<i>Staphylococcus haemolyticus</i> bacteremia	1
Nausea, fever, rash due to ATG	1
Neutropenic fever, mucositis, coagulopathy	1
Transient upper right limb edema during conditioning (no signs of thrombosis)	1
Pneumothorax after CVC insertion	1
Skin rash, neutropenic fever	1
Gastric tract symptoms, fever	1
Alopecia, fever, failure of stem cell harvest	1
<i>Pseudomonas aeruginosa</i> sepsis	1
Alopecia, gastric tract symptoms, nutrition support	1
Alopecia, fever, hematuria	1
Gastric tract symptoms, fever, bone marrow suppression	1
Gastric tract symptoms, granulocyte suppression	1
Diarrhea	1
<b>Total number of subjects experiencing adverse effects</b>	<b>34/65</b>

ATG, antithymocyte globulin; CVC, central venous catheter; DIC, disseminated intravascular coagulation.

improvement in both glycometabolic status and  $\beta$ -cell function compared with poor responders, who continued insulin treatment over time. However, the occurrence of some severe adverse events advocates for caution in selecting T1D individuals to be enrolled in this treatment protocol and does not suggest that the current protocol, without any modifications, can be used for a broader group of individuals with T1D. In particular, it is evident that the majority of adverse events, such as neutropenic fever and pulmonary infections, resulted from the administration of a high-dose immunosuppressive regimen, although immune recovery was achieved after AHSCT. This observation may indicate the need for reducing the dosage in the immunosuppressive regimen or for eventually changing the immunosuppressive agents being administered and for a stronger prophylaxis for infections to obtain a safer approach. Nevertheless, a combination treatment, potentially based on the administration of stem cells and immunosuppression, will most likely be required to treat individuals with T1D. Moreover, the need for injecting autologous CD34<sup>+</sup> cells into individuals with T1D raises the following two major issues: the appropriate mobilization of CD34<sup>+</sup> cells in T1D patients; and the appropriate number of cells to be injected. It has been shown that stem cell and proangiogenic cell



mobilization in response to G-CSF is impaired in individuals with T1D (21), thus questioning whether alternative approaches such as the use of a C-X-C chemokine receptor type 4 inhibitor (plerixafor), which is already in use in the field of hematology (22), should be explored to mobilize a sufficient number of cells to be injected in individuals with T1D (23). Finally, the number of but also the type of injected cells is an important issue. Our results demonstrate that the response to AHSTC and the beneficial effects on glycometabolic control strictly depend on the number of CD34<sup>+</sup> cells injected. The effectiveness of AHSTC in treating patients with T1D relies on previously described immunoregulatory properties of CD34<sup>+</sup> cells (24); however, it is possible that subsets of HSCs exert greater immunomodulatory function and that the infusion of a limited number of selected HSCs will be required in the near future. The occurrence of severe adverse events in treated subjects also highlighted the fact that AHSTC may represent a potential therapeutic approach for selected individuals with T1D but is most likely not suitable for all subjects.

In conclusion, our study suggests the following: 1) that remission of T1D is possible; 2) that a combination therapy is possibly needed; 3) that AHSTC represents an effective treatment for selected individuals with T1D; and 4) that safer HSC-based therapeutic options are required, including engineering of HSCs based on recently novel immunoregulatory pathways (25).

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**Author Contributions.** F.D. and A.V.V. analyzed the data and wrote the manuscript. M.B.N. analyzed the data. E.F., D.Z., L.L., and G.N. performed research. E.S. performed research and analyzed the data. P.F. designed the research and wrote and edited the manuscript. P.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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