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Preliminary Communication

Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation in Newly Diagnosed Type 1 Diabetes Mellitus

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ABSTRACT

Context Type 1 diabetes mellitus (DM) results from a cell-mediated autoimmune attack against pancreatic beta cells. Previous animal and clinical studies suggest that moderate immunosuppression in newly diagnosed type 1 DM can prevent further loss of insulin production and can reduce insulin needs.

Objective To determine the safety and metabolic effects of high-dose immunosuppression followed by autologous nonmyeloablative hematopoietic stem cell transplantation (AHST) in newly diagnosed type 1 DM.

Design, Setting, and Participants A prospective phase 1/2 study of 15 patients with type 1 D 14-31 years) diagnosed within the previous 6 weeks by clinical findings and hyperglycemia and with positive antibodies against glutamic acid decarboxylase. Enrollment was November 2003-Ju with observation until February 2007 at the Bone Marrow Transplantation Unit of the School of M Ribeirão Preto, Ribeirão Preto, Brazil. Patients with previous diabetic ketoacidosis were excluded first patient with diabetic ketoacidosis failed to benefit from AHST. Hematopoietic stem cells wer mobilized with cyclophosphamide (2.0 g/m^2) and granulocyte colony-stimulating factor (10 µg/k and then collected from peripheral blood by leukapheresis and cryopreserved. The cells were inj intravenously after conditioning with cyclophosphamide (200 mg/kg) and rabbit antithymocyte g (4.5 mg/kg).

Main Outcome Measures Morbidity and mortality from transplantation and temporal changes exogenous insulin requirements (daily dose and duration of usage). Secondary end points: seru hemoglobin A_{1c}, C-peptide levels during the mixed-meal tolerance test, and anti–glutamic acid decarboxylase antibody titers measured before and at different times following AHST.

Results During a 7- to 36-month follow-up (mean 18.8), 14 patients became insulin-free (1 fo months, 4 for at least 21 months, 7 for at least 6 months; and 2 with late response were insulin

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and 5 months, respectively). Among those, 1 patient resumed insulin use 1 year after AHST. At after AHST, mean total area under the C-peptide response curve was significantly greater than t pretreatment values, and at 12 and 24 months it did not change. Anti–glutamic acid decarboxyla antibody levels decreased after 6 months and stabilized at 12 and 24 months. Serum levels of h A_{1c} were maintained at less than 7% in 13 of 14 patients. The only acute severe adverse effect culture-negative bilateral pneumonia in 1 patient and late endocrine dysfunction (hypothyroidisr hypogonadism) in 2 others. There was no mortality.

Conclusions High-dose immunosuppression and AHST were performed with acceptable toxicity number of patients with newly diagnosed type 1 DM. With AHST, beta cell function was increase 1 patient and induced prolonged insulin independence in the majority of the patients.

Trial Registration clinicaltrials.gov Identifier: NCT00315133

INTRODUCTION

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Type 1 diabetes mellitus (DM) results from a cell-mediated autoimmune attack against pancreatic beta cells.[1] The course of autodestruction is subclinical until the amount of beta-cell mass is insufficient to maintain glucose homeostasis. Thus, at the time of clinical diagnosis, approximately 60% to 80% of the beta-cell mass has been destroyed.[2]

Type 1 DM comprises only 5% to 10% of all diabetic etiologies but is associated with a high freq vascular complications and compromises quality and expectancy of life.[3-4] Patients with type 1 D on exogenous insulin administration for survival and for control of long-term complications. The established treatment is tight control of blood glucose achieved by frequent daily injections or cc subcutaneous infusion of insulin, ie, intensive insulin therapy. This treatment reduces the risk of retinopathy, nephropathy, and neuropathy by 35% to 90% when compared with conventional th with 1 to 2 injections per day.[5]

Subgroup analysis of the Diabetes Control and Complications Trial showed that patients with a la cell reserve demonstrable by serum C-peptide levels presented a slower decline of these levels c study and experienced fewer microvascular complications than patients with low or undetectable peptide concentrations. Therefore, beta cell preservation is another important target in the mana of type 1 DM and in the prevention of its related complications.[6]

Many clinical trials have evaluated the role of immunointervention in preventing residual beta ce blocking the autoimmune response with prednisone,[7] azathioprine,[8-9] prednisone plus azathiopri cyclosporine,[11] antibodies against CD3,[12-13] heat shock protein,[14] and rabbit antithymocyte glob These therapies were shown to induce a slower decline or some improvement in C-peptide levels compared with placebo groups. However, almost all patients required exogenous insulin use.

Since 1996, organ-threatening systemic lupus erythematosus[16] and other autoimmune diseases been successfully treated with high-dose immunosuppression followed by autologous nonmyeloa hematopoietic stem cell transplantation (AHST). Organ function was salvaged and in many cases following AHST. In animal models, allogeneic bone marrow transplantation prevents both insuliti development of type 1 DM in susceptible strains of mice.[18]

On the basis of these observations, we initiated a phase 1/2 study in November 2003 analyzing metabolic effects, and ability of AHST to preserve beta cell function in patients with newly diagn 1 DM. Here we report the first prospective trial, to our knowledge, of stem cell therapy in humar describe 15 patients with type 1 DM, submitted to AHST, and observed from 7 to 36 months (m months) after treatment.

METHODS

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Patients

Inclusion criteria were patients of both sexes, aged 12 to 35 years, with a diagnosis of type 1 DM during the previous 6 weeks confirmed by measurement of serum levels of anti–glutamic acid decarboxylase (anti-GAD) antibodies. From September 2003 to February 2007, more than 100 patients were offered screening for enrollment (most by e-mail or telephone interviews). Of those patients, 52 fulfilled the inclusion criteria and were personally interviewed, 15 patients opted to participate, a were subsequently enrolled between November 2003 and July 2006 and observed until February the Bone Marrow Transplantation Unit of the School of Medicine of Ribeirão Preto, Ribeirão Preto

The main reasons for not fitting the inclusion criteria were the duration of type 1 DM longer thar or previous episodes of diabetic ketoacidosis. Concerns about the probable adverse effects relate immunosuppression were the main cause of refusing study participation. The first patient enrolle diagnosed with diabetic ketoacidosis and received hydrocortisone (200 mg) and methylprednisol mg) to prevent rabbit antithymocyte globulin reactions. This patient's continued insulin depende AHST (see Results section) resulted in modification of the protocol to exclude patients with diabe ketoacidosis-onset diabetes and to remove glucocorticoids from the immunosuppression regimer exclusion criteria were positive serology for human immunodeficiency virus, hepatitis B or C, an underlying hematologic, nephrologic, cardiac, psychiatric or hepatic disease. Serum levels of β-h chorionic gonadotropin were determined in all women to exclude pregnancy.

Participants were initially treated by their own physicians until admission to the present study. Race/ethnicity was self-reported and was assessed because of the diversity of the Brazilian popu along with its prevalence of black/white biracialiy. HLA class II typing was performed at low/mec resolution using reverse sequence-specific oligonucleotide probes (RSSOP-One Lambda, Canoga Calif), and at high resolution using sequence–specific primers (SSP, One Lambda). The study pro approved by the research ethics committees of both the University Hospital of the School of Med Ribeirão Preto and the Brazilian Ministry of Health. An informed consent according to the Declara Helsinki was signed by patients or their parents.

Study Design

Key end points of the study were morbidity and mortality from transplantation and temporal cha exogenous insulin requirements (daily dose and duration of usage). Secondary end points were s levels of hemoglobin A_{1c}, C-peptide levels during the mixed-meal tolerance test, and anti-GAD a titers measured before and at different times following transplantation.

Blood samples for hemoglobin A_{1c} determination were collected after an 8-hour fast at pretreatn every 3 months thereafter. Blood samples for the determination of C-peptide, an indirect measu endogenous insulin secretion, were collected in the fasting state and every 30 minutes during a

mixed-meal tolerance test. The morning and evening doses of insulin were withheld the day befo test at pretreatment, 6 months, 1 year and then yearly following AHST. Serum anti-GAD antibod titrated at the same intervals.

All patients were encouraged to self-monitor blood glucose at least twice daily (before and 2 hou different meals and/or at 3 AM) between mobilization and the conditioning phase and then indefi discharge from the hospital. During hospitalization, blood glucose monitoring was performed bef and at bedtime. Insulin titration was based on fasting before meals and 2 hours after meals with blood glucose levels of less than 120 mg/dL (6.7 mmol/L) and less than 140 mg/dL (7.7 mmol/L respectively. The dose of insulin was reduced by 1-2 IU/mL if patients presented clinical findings hypoglycemia and/or blood glucose levels less than 4.9 mmol/L (90 mg/dL).

Standard recommendations for lifestyle modification (performing physical activities and a low-su after AHST were made to all patients irrespective of exogenous insulin use. Intensive insulin the the treatment of choice for all patients who needed exogenous insulin. All changes in insulin dos ordered by one of the endocrinologists of the team (C.E.B.C.).

Stem Cell Mobilization Regimen

Peripheral hematopoietic stem cells were mobilized with cyclophosphamide and granulocyte colo stimulating factor (Leucin, Laboratory Bergamo, São Paulo, SP, Brazil). Cyclophosphamide (2 g/ infused in 2 doses 12 hours apart in 250 mL of saline solution over 1 hour. Uroprotection was ac with intravenous saline infusion at 250 mL/h, initiated 4 hours before cyclophosphamide infusion continued for 16 hours. Mesna (sodium 2-mercaptoethanesulfonate), 4 g/m^2, was infused over 2 to bind toxic cyclophosphamide metabolites in the bladder. Granulocyte colony-stimulating facto µg/kg per day) was injected subcutaneously starting 1 day after cyclophosphamide infusion and continuing until leukapheresis was completed.

Leukapheresis using a continuous-flow blood cell separator was initiated when the rebounding C reached 10 cells/µL. Apheresis was continued daily until the number of harvested progenitor cell a minimum of 3.0 x 10^6 $CD34^+$ cells/kg body weight. Unmanipulated peripheral blood stem cells frozen in 10% dimethyl sulfoxide in a rate-controlled freezer and stored in the vapor phase of liq nitrogen.

Conditioning (Immune Ablative) Regimen

Conditioning was achieved with cyclophosphamide and antithymocyte globulin. Cyclophosphamid given intravenously in divided doses of 50 mg/kg per day over 1 hour on days 5, 4, 3, and 2 bef cell infusion. Rabbit antithymocyte globulin (thymoglobulin, IMTIX Sangstat, Lyon, France) was administered at a dose of 0.5 mg/kg per day on day 5 before, and at a dose of 1 mg/kg per day 4, 3, 2, and 1 before stem cell infusion. Except for the first patient, prophylaxis of antithymocyte reactions was done with dexchlorpheniramine (6 mg by mouth) avoiding the use of glucocorticoi cell infusion was performed on day 0 and granulocyte colony-stimulating factor (5 µg/kg per day administered subcutaneously from day 5 after stem cell infusion until neutrophil count was great 1000/µL.

Supportive Care

Patients were isolated in rooms equipped with high-efficiency particulate air filters. After hospita admittance for conditioning, antimicrobial prophylaxis was started with ciprofloxacin (500 mg ev

hours intravenously), acyclovir (250 mg/m^2 every 8 hours by mouth until day 35), amphotericin mg/kg per day intravenously and 10 mg/d aerosolized). Ciprofloxacin was replaced by cefepime 12 hours intravenously) during febrile episodes. After engraftment, antifungal prophylaxis was c fluconazole (400 mg/d by mouth until day 60) and sulfamethoxazole/trimethoprim (800/160 mg hours by mouth 2 times per week) or dapsone (100 mg 3 times per week) was given through da prevention of *Pneumocystis jiroveci* pneumonia. Weekly monitoring of cytomegalovirus antigene circulating neutrophils was performed until day 60.

During pretreatment evaluation, semen samples were collected and frozen in liquid nitrogen. Le acetate depot (3.75 mg by intramuscular injection) was given to female patients to prevent men bleeding and to protect ovarian function. All women opted to use oral contraceptive methods aft

Laboratory Assessment of Diabetic Status

Serum C-peptide levels were measured by radioimmunoassay using commercial kits (Diagnostic Laboratories Inc, Webster, Tex). The lower limit of detection was 0.1 ng/mL and undetected valu reported as 0.1 ng/mL. Serum levels of anti-GAD antibodies were measured by radioimmunoass commercial kits (RSR Limited, Cardiff, UK) and the results were considered positive if greater th U/mL. Hemoglobin A_{1c} was measured by low-pressure liquid chromatography.

Statistical Analysis

Multiple comparisons of total area under the curve of serum C-peptide measured during the mix tolerance test (during fasting and at 30, 60, 90, and 120 minutes) were made using a model of regression of mixed effects for periods 0, 6, 12, and 24 months posttransplantation. The same m used to test anti-GAD titers. To present the mean variation of hemoglobin A_{1c} levels with time, a linear regression of random effects was constructed using the following equation: $y = \beta_0 + \beta_1 \times l$ (time) + $\beta_2 \times$ [log (time)]^2, in which each parameter represents a random effect in each patient. models are characterized to present residuals that are normally distributed. Data analysis was c using PROC MIXED, SAS statistical software, version 8 (SAS Institute Inc, Cary, NC).

RESULTS

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Fifteen patients aged 14 to 31 years (mean 19.2 years) were enrolled in the study between November 2003 and July 2006. Individual demographic characteristics and follow-up variables are listed in Table 1 and Table 2. Mean body mass index (calculated as weight in kilograms divided by height in meters squared) at diagnosis was 19.8 (range, 16.6-23.4) and mean plasma glucose was 391 mg/dL (21.7 mmol/L) (range, 130-612 mg/dL [7.2-33.9 mmol/L]). All patients presented symptoms of hyperglycemia (polyuria, polydipsia, and weight loss) at diagnosis. Six patients pre both HLA haplotypes characteristic of high risk for type 1 DM, 7 patients presented 1 of those ha and 2 patients presented 0.

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Table 1. Pretreatment and Follow-up Variables of Patients With Type 1 D Mellitus Undergoing Autologous Nonmyeloablative Hematopoietic Stem Ce Transplantation (Patient Demographics, HLA Type, Blood Glucose, Hemog

A_{1c}, Weight Loss, Hyperglycemia Symptoms, Body Mass Index)

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Table 2. Pretreatment and Follow-up Variables of Type 1 Diabetic Patient Undergoing Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation (Anti–Glutamic Acid Decarboxylase, C-Peptide, Insulin Do Insulin-Discontinuation Time, Insulin-Free Time)

Time from diagnosis to mobilization ranged from 25 to 56 days (mean, 38.4) and mean duration hospital stay for transplantation (from conditioning to discharge) was 19.2 days (range, 15-24). number of infused $CD34^+$ cells was 11.0 x 10^6/kg (range, 5.8-23.1 x 10^6/kg). Neutrophil engraft (>500/µL) occurred between days 8 and 10 after transplantation (mean 9.1 days) and platelet engraftment (>20 000/µL) was detected between day 0 and day 15 after transplantation (mean days).

Most patients had febrile neutropenia, nausea, vomiting, alopecia, and other common transplant related complications due to the drugs used in the mobilization and conditioning (Table 3). Bilate pneumonia of unidentified etiology that required supplementary oxygen therapy and responded completely to broad-spectrum antibiotics occurred in patient 2 and was the only severe acute co of AHST. During long-term follow-up, patient 3 developed autoimmune hypothyroidism and tran dysfunction associated with rhabdomyolysis, a complication that was treated successfully with levothyroxine. Measurements of gonadal function (follicle-stimulating hormone and lutenizing ho both sexes, testosterone in men, and estradiol in women) were in the normal range in 14 of 15 Patient 2 fathered a child 2 years after transplantation (by natural means) and patient 10 preser hypergonadotropic hypogonadism at 12 months following transplantation. There was no mortalit

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Table 3. Transplantation Complications and Gonadal Function Tests*

The first patient enrolled in the study presented few minor complications of transplantation (Tab However, this patient's insulin requirements increased progressively and at 12 months following transplantation when he abandoned follow-up, he was using a dose 250% higher than his initial requirement (1.7 IU/kg per day). His hemoglobin A_{1c} levels were 7.6%, 8.2%, 8.9%, 9.7%, and 0, 3, 6, 9, and 12 months following transplantation, respectively, and his C-peptide levels were study entry (basal level, 0.4 ng/mL; peak stimulated level, not available) and did not increase at (basal, 0.3 ng/mL; peak stimulated level, 0.4 ng/mL) (Table 1 and Table 2). Anti-GAD antibody were 36.0, 9.9, and 7.7 U/mL at 0, 6, and 12 months following transplantation, respectively. Sir protocol was changed after treating this patient, his data were not included in the statistical ana Thus, hemoglobin A_{1c} (Figure 1) and results of C-peptide levels (Figure 2) refers to 14 patients f the same selection criteria and receiving the same conditioning regimen.

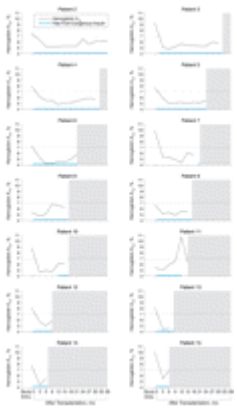

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Figure 1. Hemoglobin A_{1c} Levels and Periods Free From Exogenous Insulin Requirement

Data from patient 1 were not included. Mean hemoglobin values were adjusted with a model of linear regression of effects based on the following equation: $y = 7.8185 - 2.4237 \times \log(\text{time}) + 0.5512 \times [\log(\text{time})]^2$. Differences between pretransplantation and all posttransplantation le were statistically significant ($P<.05$). Horizontal dotted lir indicate hemoglobin A_{1c} treatment goal < 7%. Gray tint i end of follow-up.

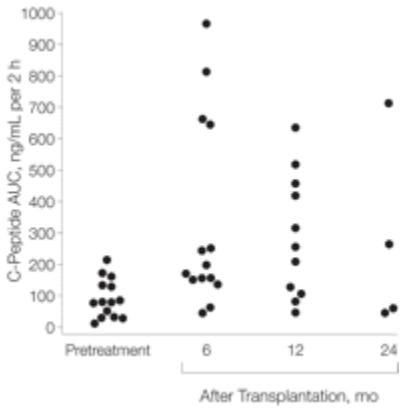

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Figure 2. Time Course of Total Area Under the Curve of Peptide Levels During Mixed-Meal Tolerance Test

Data from patient 1 were not included. Statistical analysi performed using a model of multiple regression of mixed $P<.001$ between pretreatment and 6 months; $P = .85$ be and 12 months; $P = .18$ between 12 and 24 months follo transplantation. SI conversion factor: to convert C-peptic nmol/L, multiply by 0.331.

Before the mobilization regimen, all patients required exogenous insulin (mean, 0.38 IU/kg per range, 0.13-0.58). By February 2007, 13 patients were free from exogenous insulin for 1 to 35 (mean, 16.2) (Table 2). Patient 7 used a fraction of the initial insulin dose for 20 months and dis insulin use in January 2007. Patient 10 discontinued insulin transiently during transplantation (fr before to 7 days after), then resumed insulin use (0.34 IU/kg per day) and after progressive red its dose discontinued insulin again 1 year after transplantation. Patient 11 was free from insulin days before transplantation until 360 days after,when insulin use was resumed (0.43 IU/kg per an upper respiratory tract viral infection. The time course of individual insulin doses in different presented in Table 2.

All 14 patients treated according to the same protocol (patients 2-15) complied with blood gluco monitoring and scheduled medical appointments. The time course of hemoglobin A_{1c} concentrati those patients is presented in Figure 1. There was a statistically significant reduction of hemoglo levels after transplantation. At entry into the study, 11 of 14 patients presented values above 7

within 3 months after AHST, hemoglobin A_{1c} values were below this level and were maintained c follow-up (except for the relapsing patient 11).

The time course of fasting and peak stimulated C-peptide levels and of the area under the curve curve during mixed-meal tolerance test are shown in Table 2 and Figure 2. Compared with pretr levels, peak stimulated C-peptide levels following transplantation increased in 11 of 13 patients 6 months, in 8 of 10 patients studied at 12 months, in 4 of 4 patients studied at 24 months, and patient studied at 36 months. Mean peak stimulated C-peptide levels were 1.3 ng/mL at pretrea following transplantation 4.0 ng/mL at 6 months, 3.7 ng/mL at 12 months, and 4.5 ng/mL at 24 The increase at 24 months following transplantation was statistically significant compared with a time points (Table 2). Mean area under the curve of C-peptide levels before transplantation (92. per 2 hours) showed a statistically significant increase at 6 months following transplantation (33 per 2 hours), which was not different from 12 months (289.2 ng/mL per 2 hours) and 24 month ng/mL per 2 hours) (Figure 2).

Mean values of anti-GAD antibodies at diagnosis and at 6, 12, and 24 months after treatment w U/mL, 17.3 U/mL, 12.5 U/mL, and 18.7 U/mL, respectively (Table 2). Statistical differences were between pre- and and post-6-month titers but not among posttreatment times. Anti-GAD titers negative in only 1 patient (patient 3) at 6 months posttreatment, and continued to show as nega the 2-year-follow-up.

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Many clinical trials have analyzed the effect of various immunointervention regimens in blocking autoimmune response and preserving beta-cell function. Short chronic use (≤12 months) of prednisone,[7] azathioprine,[8-9] azathioprine plus prednisone,[10] and cyclosporine[11] in randomized controlled trials produced variable degrees of improvement in C-peptide levels at the end of follow-up compared with pretreatment values. However, these effects were not maintained after immunosuppression was discontinued.[7-11]

Recent studies using short-term treatment with anti-CD3 monoclonal antibodies or heat-shock p showed long-lasting improvements on C-peptide levels (up to 18 months), however with only pa improvement in insulin usage.[12-14] Control groups in the recent studies of immunointervention (with intensive insulin therapy) experienced progressive declines of C-peptide levels after study e after transient increase in its levels and a parallel increase in insulin needs.[12-15]

In our study, the increase of C-peptide levels and reduction of hemoglobin A_{1c} were maintained after insulin discontinuation, excluding the acute effect of insulin therapy on C-peptide concentra metabolic control. The natural history of type 1 DM was more altered in our study than in other immunosuppression interventions because, different from those studies, 14 of 15 or 93% of our experienced variable periods of insulin independence and most of them maintained this status th the follow-up.

Beta cell function in newly diagnosed type 1 DM is a measurable outcome that predicts long-terr status. Thus, preservation of beta-cell mass can be expected to provide long-term benefits.[6, 19] patient failed to show a clinical benefit probably because of a very low beta-cell reserve at study predicted by previous ketoacidosis that was further jeopardized by the beta-cell apoptotic effect

glucocorticoids used during conditioning.[20] Most of the subsequent 14 patients treated without glucocorticoids in the conditioning regimen demonstrated increased beta-cell function measured peptide levels and became insulin-independent for 1 to 35 months. Two patients (identified as 7 who initially remained on insulin use shortly after transplantation developed insulin independenc 12 months after AHST, respectively, probably secondary to progressive elevations in C-peptide l time. The reverse was seen in patient 11, who presented a decline in C-peptide levels after 1 ye resumed insulin use after that time. With the exception of patient 1, irrespective of insulin use a achieved and maintained peak stimulated C-peptide levels greater than 0.60 ng/mL, which is kn associated with reduced prevalence of diabetic complications.[21] Area under the curve levels of C increased significantly after transplantation and remained high up to 24 months thereafter.

All patients experienced common transplantation-related complications of high-dose immunosup and only 1 patient presented a major infectious complication. The low frequency of severe acute complications after AHST is expected in a group of young patients with early-onset type 1 DM in to other advanced autoimmune diseases.[16-17] On the other hand, 2 patients presented late endo dysfunctions that could be caused by autoimmune dysregulation associated with the transplant procedure[22] or by autoimmune polyendocrine syndrome frequently associated with type 1 DM.[23] cannot exclude the occurrence of long-term complications related to high-dose cyclophosphamid

The exact mechanism of action of AHST in autoimmune disorders is not fully understood. Wheth mechanism is active or passive tolerance, ie, T-regulatory cell suppression or clonal deletion, is u In multiple sclerosis, evidence supporting post-AHST immune resetting includes an increase in t derived naive T cells, decreased central-memory T cells, increased output of recent thymic emig recovery of a diverse but distinct T-cell receptor repertoire following AHST.[24] Detailed studies of reconstitution are underway in these patients to better understand the mechanisms of action of new-onset diabetes. Preliminary data suggest a resetting of the immune system toward a tolera phenotype beyond 1 year after transplantation, as observed in multiple sclerosis (K.C.R.M. and J unpublished data, 2006). In the patients of this study, persistence of anti-GAD antibodies, even titers, shows that the conditioning regimen was not fully ablative for autoreactive B-cell clones a confirms that the magnitude of the humoral response is not predictive of beta cell reserve or clin response.[19]

Improvement of beta-cell function after intensive immunosuppression could be explained by reg of beta cells from surviving beta cells or from pancreatic or bone marrow stem cells.[25-26] Howev pancreatic stem cells have not been clearly demonstrated, and significant in vivo generation of i from hematopoietic stem cells was not observed in animal models of type 1 DM[18] or in patients v term type 1 DM treated with allogeneic hematopoietic stem cell transplantation for concomitant disorders.[27]

This is, to our knowledge, the first report of high-dose immunosuppression followed by autologo nonmyeloablative hematopoietic stem cell transplantation for human type 1 DM. Very encouragi were obtained in a small number of patients with early-onset disease. Ninety-three percent of pa achieved different periods of insulin independence and treatment-related toxicity was low, with r mortality. Further follow-up is necessary to confirm the duration of insulin independence and the mechanisms of action of the procedure. In addition, randomized controlled trials and further biol studies are necessary to confirm the role of this treatment in changing the natural history of typ and to evaluate the contribution of hematopoietic stem cells to this change.

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Analysis and interpretation of data: Voltarelli, Couri, Stracieri, Malmegrim, Foss-Freitas, Simões, Squiers, Burt.

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