

HOW CAN WE ACCELERATE STEM CELL DERIVED THERAPIES TO THE CLINIC?

- I) UNDERSTANDING DISEASE ACCELERATES
THERAPY DEVELOPMENT
- II) ENHANCING SAFETY ACCELERATES INITIATION
OF CLINICAL TRIALS
- III) ACCURATE COMMUNICATION ACCELERATES
RESPONSIBLE CLINICAL TRIALS

UNDERSTANDING DISEASE

- ACHIEVING EFFECTIVE CELL REPLACEMENT THERAPY REQUIRES KNOWING MORE THAN JUST WHICH CELLS ARE DEFECTIVE OR DIE
- EXAMPLES OF DISEASES WHERE MULTIPLE CELL TYPES CONTRIBUTE
 - ◆ TYPE 1 DIABETES-ABERRANT IMMUNE SYSTEM
 - ◆ AMYOTROPHIC LATERAL SCLEROSIS-OTHER SPINAL CORD CELLS ARE IMPORTANT CONTRIBUTORS

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SOME SPECIAL SAFETY ISSUES WITH STEM CELLS

- AFTER CELLS ARE TRANSPLANTED, DO THEY STAY WHERE THEY WERE PUT?
 - ◆ WHERE DO THEY GO?
- WHAT IF TRANSPLANTED CELLS DO SOMETHING BAD?
 - ◆ THE CASE OF PARKINSONS DISEASE
 - ◆ THE CASE OF SEVERE COMBINED IMMUNODEFICIENCY
- *THE BOTTOM LINE-ENHANCING SAFETY IS LIKELY TO REDUCE CONCERNS ABOUT INITIATING NEW CLINICAL TRIALS WITH STEM CELLS*

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COMMUNICATING ACCURATELY

- WHAT IS A CLINICAL TRIAL?
 - ◆ A CLINICAL TRIAL IS A SERIES OF EXPERIMENTS WITH HUMAN VOLUNTEERS TO DETERMINE WHETHER A NEW THERAPY IS SAFE AND EFFECTIVE

FROM PHASE 1/2 CLINICAL TRIAL TO CURE IN A FEW HOURS

PRELIMINARY
COMMUNICATION

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

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TYPE 1 DIABETES MELLITUS (DM) results from a cell-mediated autoimmune attack against pancreatic beta cells.¹ The course of autoantibody attack against pancreatic beta cells 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 frequency of vascular complications and compromises quality and expectancy of life.^{3,4} Patients with type 1 DM depend on exogenous insulin administration for survival and for control of long-term complications. The best-established treatment is tight control of blood glucose achieved by frequent daily injections or continuous subcutaneous in-

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 DM (aged 14-31 years) diagnosed within the previous 6 weeks by clinical findings and hyperglycemia and confirmed with positive antibodies against glutamic acid decarboxylase. Enrollment was November 2003-July 2006 with observation until February 2007 at the Bone Marrow Transplantation Unit of the School of Medicine of Ribeirão Preto, Ribeirão Preto, Brazil. Patients with previous diabetic ketoacidosis were excluded after the first patient with diabetic ketoacidosis failed to benefit from AHST. Hematopoietic stem cells were mobilized with cyclophosphamide (2.0 g/m²) and granulocyte colony-stimulating factor (10 µg/kg per day) and then collected from peripheral blood by leukapheresis and cryopreserved. The cells were injected intravenously after conditioning with cyclophosphamide (200 mg/kg) and rabbit antihymocytic globulin (4.5 mg/kg).

Main Outcome Measures Morbidity and mortality from transplantation and temporal changes in exogenous insulin requirements (daily dose and duration of usage). Secondary end points: serum levels of 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 for 35 months, 4 for at least 21 months, 7 for at least 6 months; and 2 with late response were insulin-free for 1 and 5 months, respectively). Among those, 1 patient resumed insulin use 1 year after AHST. At 6 months after AHST, mean total area under the C-peptide response curve was significantly greater than the pre-treatment values, and at 12 and 24 months, it did not change. Anti-glutamic acid decarboxylase antibody levels decreased after 6 months and stabilized at 12 and 24 months. Serum levels of hemoglobin A_{1c} were maintained at less than 7% in 13 of 14 patients. The only acute severe adverse effect was culture-negative bilateral pneumonia in 1 patient and late endocrine dysfunction (hypothyroidism or hypogonadism) in 2 others. There was no mortality.

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

Trial Registration clinicaltrials.gov Identifier: NCT00315133

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For editorial comment see p 1599.

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EDITORIAL

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Cellular Therapy for Type 1 Diabetes Has the Time Come?

Jay S. Skyler, MD

In the 1990s, several groups examined the potential use of BMT for type 1 DM, particularly focusing on animal models to

JAMA 297:1599 (2007)

TIMES ONLINE



“Expectations are an important part of political warfare” David Davis

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From The Times

April 11, 2007

Diabetics cured in stem-cell treatment advance

David Rose

Diabetics using stem-cell therapy have been able to stop taking insulin injections for the first time, after their bodies started to produce the hormone naturally again.

In a breakthrough trial, 15 young patients with newly diagnosed type 1 diabetes were given drugs to suppress their immune systems followed by transfusions of stem cells drawn from their own blood.

The results show that insulin-dependent diabetics can be freed from reliance on needles by an injection of their own stem cells. The therapy could signal a revolution in the treatment of the condition, which affects more than 300,000 Britons.

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A SERIOUS ALTERNATIVE

- FIND BETTER DRUGS FASTER WITH HUMAN CELLS?