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REVIEW ARTICLE

Novel therapy for type 1 diabetes: Autologous hematopoietic stem cell transplantation

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Abstract Type 1 diabetes is characterized pathologically by autoimmune insulitis-related islet β-cell destruction. Although intensive insulin therapy for patients with type 1 diabetes can correct hyperglycemia, this therapy does not prevent all diabetes-related complications. Recent studies have shown that autologous hematopoietic stem cell transplantation (HSCT) is a promising new approach for the treatment of type 1 diabetes by reconstitution of immunotolerance and preservation of islet β-cell function. Herein we discuss the therapeutic efficacy and potential mechanisms underlying the action of HSCT and other perspectives in the clinical management of type 1 diabetes.

Keywords: autologous hematopoietic stem cells, transplantation, type 1 diabetes.

IN-DEPTH VIEW

Introduction to Type 1 diabetes

Type 1 diabetes results from an autoimmune attack against islet β-cells,[1] which itself causes absolute insulin deficiency. Patients with type 1 diabetes suffer from a high frequency of vascular complications.[2,3] Because serum levels of C-peptide, representing islet β-cell function, in patients with type 1 diabetes are negatively correlated with the probability of developing chronic complications,[4,5] the development of new therapies to preserve remaining β-cell function is an important target in the management of patients with type 1 diabetes.

Autologous non-myeloablative hematopoietic stem cell transplantation: A novel therapy for type 1 diabetes

Immunosuppressants for type 1 diabetes

The autoimmune etiology of type 1 diabetes was identified in the late 1970s.[6] Since then, starting in the early 1980s,[7,8] many clinical trials have been conducted into the use of immunosuppressants, such as prednisone,[9] azathioprine,[10,11] prednisone plus azathioprine,[12] cyclosporine,[13–19] antibodies against CD3,[20,21] and rabbit antithymocyte globulin (rATG),[22] in the treatment of patients with new-onset type 1 diabetes. Although these treatment regimens inhibit autoimmune responses and improve β-cell function, immunosuppressant treatment with does not result in independence of exogenous insulin in patients with type 1 diabetes. In addition, the chronic toxicity commonly associated with immunosuppressive agents and the loss of the metabolic effects after withdrawal limits their clinical use.

Immunosuprressants combined with hematopoietic stem cell transplantation

Hematopoietic stem cells (HSCs) are multipotent stem cells residing in the bone marrow. They have durable self-renewal and differentiation properties, and are able to differentiate into different lineages of blood cells, including the myeloid monocytes and macrophages, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes/platelets, dendritic cells, and lymphoid T cells, B cells, and natural killer (NK) cells. More interestingly, HSCs also have the potential to correct and/or re-educate the immune aberration[23–25] that promotes the autoimmune attacks against self tissue. Therefore, HSC transplantation (HSCT), aiming to induce medication-free remission from active disease, is being used as a therapeutic strategy for different types of autoimmune diseases,

including multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, and type 1 diabetes.[26]

The HSCT procedure consists of three stages: (i) stimulation of HSC mobilization from the bone marrow to the peripheral blood by intravenous administration of a small dose of cyclophosphamide; (ii) conditioning of recipients by intravenous injection of different doses of immunosuppressive agents and/or total body irradiation; and (iii) re-infusing HSCs collected previously to reconstitute a new immune system without pathogenic immune memory.[27]

Depending on the design of the conditioning regimen, there are two basic HSCT protocols, myeloablative and non-myeloablative transplantation. The main difference between these two protocols is the intensity of chemotherapy and irradiation prior to the infusion of HSCs, thus resulting in different degrees of myeloablation. With the myeloablative protocol, both myeloid and lymphoid cells in the bone marrow are ablated, rendering patients at high risk of serious infection and cancers. In contrast, with the non-myeloablative protocol only lymphoid cells are ablated, lowering the risk of conditioning-related morbidity or mortality.[26]

Compared with immunosuppressive therapy alone, the addition of infused peripheral blood HSCs may decrease the risk of serious infections by shortening the duration of neutropenia and positively regulating the reconstitution of a naïve immune system. Alternatively, the combination of immunosuppression and HSC infusion may act synergistically to downregulate autoreactive cells, to reconstitute the immune system, and to modulate immune regulatory networks. Hence, HSCT after the administration of different doses of immunosuppressants has become the preferred strategy for the treatment of patients with autoimmune diseases, including type 1 diabetes.[26]

The use of HSCT as a therapeutic strategy for patients with an autoimmune disease began in 1996.[28] Autologous HSCT has been used for the treatment of most patients with autoimmune diseases because allogeneic HSCT has been associated with an increased risk of developing severe graft-versus-host disease (GVHD) and increased mortality.[27]

Rationale for using HSCT in type 1 diabetes

What are the exact mechanisms underlying the action of HSCT in type 1 diabetes? Previous studies in animal models have proposed mechanisms by which autologous and allogenic HSCT inhibit the progression of type 1 diabetes, including the suggestions that: (i) the myeloablation associated with conditioning regimens may reduce peripheral self-reactive T cells ("immune elimination") and reverse the diabetogenic autoimmune response, thereby halting the process of islet β-cell destruction;[26] (ii) HSCT reconstitutes a new adaptive immune system with a naïve T cell pool, which would not contribute to the pathogenesis of type 1 diabetes in the absence of the environmental triggers;[26] (iii) infusion of HSCs following conditioning may modulate the peripheral immunocompetent cells ("immune resetting") and, when exposed to environmental triggers, such as infections, the reconstituted immunocompetent cells present a more self-tolerant phenotype characterized by increased numbers of $CD4^+CD25^+FoxP3^+$ T cells,[29,30] thereby shifting the balance from immune destruction to immune tolerance by altering cytokine and β-cell antigen-specific humoral responses;[28,31] and (iv) HSCs may preserve islet β-cell function by stimulating β-cell regeneration, enhancing neovascularization, promoting the differentiation of progenitor cells into β-cells, and protecting β-cells against apoptosis.[32–34]

Notably, although allogenic HSCT is associated with an increased risk of developing GVHD, it still has some advantages over autologous HSCT. The replacement of the diabetic lymphohematopoietic system with cell populations derived from theoretically diabetes-resistant donors and the introduction of donor-specific tolerance may reduce the risk of the reoccurrence of autoimmunity.[35–37] Furthermore, cotransplantation of HSCT with pancreatic islets from the same donors is practical and may effectively preserve islet β-cell function, as well as extending the period of clinical remission.[38]

Evidence from animal models

There are two types of animal models of type 1 diabetes that are routinely used. The first is non-obese diabetic (NOD) mice, which are genetically predetermined and spontaneously develop autoimmune insulitis, with the onset of type 1 diabetes-related symptoms around 13–15 weeks of age. The second is experimentally induced diabetic mice, created by injecting multiple small doses of streptozotocin (STZ) or cyclophosphamide to induce autoimmune insulitis following β-cell injury.[27]

Interestingly, allogeneic, but not autogenic, HSCT halts autoimmune progression in diabetic NOD mice.[39,40] However, allogeneic HSCT does not result in euglycemia in the recipients because there are few functional islet β-cells in the mice. The cotransplantation of pancreatic islets with allogeneic HSCs from the same donor leads to euglycemia in NOD mice.[36,38,41] Apparently, allogenic HSCT has little effect on stimulating islet β-cell regeneration in diabetic NOD mice.[27]

In contrast with the situation in NOD mice, transplantation with syngeneic bone marrow cells from diabetic or normal mice re-establishes euglycemia in the STZ-diabetic mice and is associated with an increased frequency of peripheral $CD4^+CD25^+FoxP3^+$ T cells in mice.[42]

Evidence from clinical trials

In the clinic, allogenic HSCT is seldom conducted for the treatment of patients with type 1 diabetes because of the potential risk of GVHD and severe adverse events. There is one retrospective report from Seattle in which the effects of allogenic HSCT (from either human leukocyte antigen (HLA) identical or syngeneic donors) on the metabolic control of three patients with long-established type 1 diabetes who receive this treatment for hematological diseases were investigated.[43] Unfortunately, none of the three patients achieved exogenous insulin independence following transplantation, thus providing further support for the notion that the remaining islet β-cell mass is the crucial regulator of the effects of HSCT.

A cooperative study started in Brazil in 2003 (NCT00315133)

Dr Richard K Burt from Northwestern University (Chicago, IL, USA), Dr Júlio Voltarelli and others from the University of São Paulo (Ribeirão Preto, Brazil) initiated a study of autologous HSCT using a standard non-myeloablative protocol. The aim of this regimen was to prevent the autoimmune destruction of β-cells with immunosuppressive drugs (cyclophosphamide and rATG) and to reconstitute a "new" adaptive immune system from autologous HSCs.[44,45]

Both male and female patients (aged 12–35 years) were included in the study. These patients all had a duration of <6 weeks since the diagnosis of type 1 diabetes and were positive for serum glutamic acid decarboxylase antibody (GADA). From November 2003 to April 2008, a total of 23 patients was recruited to the study and subjected to autologous HSCT. Over the course of the 7–58-month follow-up period, three patients did not respond to HSCT, and these patients either accidentally received corticosteroids or had diabetic ketoacidosis (DKA) at onset, probably due to a severe depletion of islet cells. The remaining 20 patients achieved exogenous insulin independence. Twelve patients were independent of exogenous insulin for 14–52 months. Eight patients subsequently resumed exogenous insulin at a low dose (0.1–0.3 IU/kg) and two became dependent on exogenous insulin again after administration of sitagliptin, a glucagon-like peptide-1-sparing agent. More importantly, autologous HSCT significantly improved the metabolic control in all 20 patients who achieved transient or long-term exogenous insulin independence, as indicated by normal serum HbA1c levels and increased serum C-peptide levels.

With respect to adverse events, all patients with autologous HSCT survived. Two patients developed bilateral nosocomial pneumonia, three patients developed late endocrine dysfunction, and nine patients developed oligospermia.

Autologous HSCT for the treatment of newly diagnosed Chinese type 1 diabetes patients with and without DKA at onset

There are two clinical trial studies registered with ClinicalTrials.gov currently underway in China. One trial was initiated by Dalong Zhu from Drum Tower Hospital in 2006 (Nanjing), and the other was started by Guang Ning from Ruijin Hospital in 2008 (Shanghai).

Nanjing clinical trial (NCT01341899). The clinical trail in Nanjing included patients who met the following inclusion criteria: developing type 1 diabetes-related symptoms within 12 months of diagnosis; <25 years of age at time of diagnosis; and positive for at least one of GADA, protein tyrosine phosphatase antibody (IA–2A), islet cell antibody (ICA), or insulin autoantibody (IAAs). From July 2006 to July 2008, a total of 15 patients was enrolled in the trial and treated with autologous HSCT.[46]

Over the course of the 31–54-month follow-up period, 11 patients exhibited decreased HbA1c levels and increased C-peptide levels at different time points following HSCT. Three of 11 patients achieved exogenous insulin independence and maintained this status for 7 months, >3 and 4 years. The remaining eight patients required a significantly reduced dose of exogenous insulin after HSCT.[46] There were no severe adverse effects, such as mortality, hemorrhagic cystitis, or severe infection, in any patient.

Notably, although DKA is considered by Drs Burt and Voltarelli as a key factor for the failure of HSCT, two of the three patients in the Nanjing trial with ketoacidosis at onset of diabetes achieved exogenous insulin independence following autologous HSCT. These data suggest that HSCT may still be valuable for newly diagnosed type 1 diabetes patients, even those with DKA. Coincidently, Voltarelli et al. initiated a similar protocol in new-onset type 1 diabetes patients with previous DKA in 2007,[27] but only one patient had been enrolled in the study by January 2008.[27] Although this patient did not achieve insulin independence, the insulin doses required were reduced by approximately 40%.[27]

Shanghai clinical trial (NCT00807651). The inclusion criteria for the clinical trial conducted in Shanghai were type 1 diabetes with <6 months since diagnosis and positive GADA, but no previous or current DKA.[47] By March 2010, 18 patients had been recruited to the trial, subjected to HSCT and followed-up for 8–19 months. Twelve of the 18 patients became exogenous insulin independent after autologous HSCT, but four of these patients resumed exogenous insulin after respiratory tract infection. Mean serum C-peptide levels in these 18 patients increased significantly, whereas mean GADA titers decreased significantly following HSCT. All patients presented only mild side effects, such as nausea, vomiting, fever, or alopecia immediately after treatment with cytotoxic drugs.[47]

Similar studies conducted in other research centers
In 2008, Jedrzejczak et al. (Medical University of Warsaw, Warszawa, Poland) started a protocol of autologous HSCT with inclusion and exclusion criteria similar to those of the cooperative study between Chicago and Ribeirão Preto.[48] During the mean 7 months of follow-up (range 3–16 months), all eight patients in the trial became exogenous insulin independent after HSCT, but one resumed low-dose insulin 7 months after transplantation.[50] There were no reports of severe adverse events, except for mild cytotoxic drug-related complications following the procedure of conditioning.

Limitations and future challenges

Currently, HSCT is a potential therapeutic strategy for type 1 diabetes and provides at least three advantages over both exogenous insulin medication and immunosuppressive therapies: (i) elimination of a proinflammatory immune system by the conditioning procedure may halt the ongoing process of autoimmunity-mediated destruction of islet β-cells; (ii) the HSCs infused after conditioning may generate a new adaptive immune system with the properties of immune tolerance and so the redevelopment of autoimmunity against islet β-cells may be suppressed; and (iii) the HSCs infused may stimulate the regeneration of islet β-cells, improving endogenous islet β-cell function and further delaying the development of diabetes-related chronic complications. Despite the positive results from initial studies of HSCT in type 1 diabetes, several concerns have been raised. First, this regimen may not benefit patients with long-standing type 1 diabetes because it has little effect in patients with very low serum C-peptide levels. Second, currently there are insufficient data to evaluate the risk:benefit ratio because of a lack of randomized controls with either insulin treatment alone or immunointervention, particularly given the potential for life-threatening short- and long-term complications, and the high expenditure required for the performance of the complex procedure. Third, the precise mechanisms underlying the action of HSCT are not clear, so that studies of immunoreconstitution (phenotypic and functional) and/or differentiation of progenitor cells into islet β-cells after transplantation will be of importance.

In the future, HSCT has to be tested in other groups of patients (those with previous ketoacidosis and young children), with a large number of cases and optimal controls in a population with different genetic backgrounds. In addition, further studies are needed to validate the long-term effects and safety of HSCT, as well as to determine the potential regulators of the effects of HSCT on islet β-cell function in the clinic.

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Disclosure

The authors declare no conflicts of interest.

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