Stem Cell Therapies in Diabetes Mellitus

Khalid Ahmed Al-Anazi*

Department of Hematology and Hematopoietic Stem Cell Transplantation, Oncology Center, King Fahad Specialist Hospital, Saudi Arabia

*Corresponding author: Khalid Ahmed Al-Anazi, Consultant Hemato-Oncologist and Chairman, Department of Hematology and Hematopoietic Stem Cell Transplantation, Oncology Center, King Fahad Specialist Hospital Tel: 966038431111; Fax: 966 -13- 8427420; E-mail: kaa_alanazi@yahoo.com

Received date: March 19, 2018; Accepted date: March 22, 2018; Published date: March 29, 2018

Introduction

Diabetes mellitus (DM), a chronic illness with abnormally high blood glucose affecting millions of people around the world, is associated with severe complications that can involve almost everybody organ [1-6]. DM is usually classified into: (1) type 1 DM which is associated with absolute insulin deficiency caused by autoimmune destruction of pancreatic β-cells, (2) type 2 DM which is associated with insulin resistance due to progressive insulin secretory defect in addition to immune dysfunction, and (3) other types such as gestational, drug-induced, transplant-related and monogenic DM [4,5,7-9]. The available therapeutic options for patients with DM include: diet and modifications of lifestyle, oral hypoglycemic drugs, insulin therapy as well as transplantation of pancreatic islet cell [2,6,10-12].

Islet cell transplantation (ICT) has been performed for type 1 DM since the 1990s, but it has the following disadvantages: limited access to the procedure, shortage of cadaveric donors, need for chronic immunosuppression and immune rejection leading to recurrence of autoimmune destruction of pancreatic β-cells [13-16]. Since the year 2000, more than 1500 pancreatic ICTs have been performed [17]. The exclusion of corticosteroid therapy from the Edmonton protocol led to higher response rates and longer duration of insulin independence [18]. Donor hematopoietic stem cells (HSCs) can be utilized to induce donor-specific tolerance to the graft thus allowing regeneration of the transplanted islet cells [19,20].

Stem cells are biological cells that are able to differentiate, divide, renew and repair tissues [21,22]. The main categories of stem cells include: (1) totipotent, (2) multipotent or adult cells such as mesenchymal stem cells (MSCs), and (3) pluripotent including induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs) [21,23-27]. The sources of stem cells are variable and they include: bone marrow (BM), peripheral blood (PB), umbilical cord blood (UCB), amniotic fluid, placenta, dental pulp and adipose tissue (AT) [21,23,27]. Each type of stem cells has its own flow cytometric profiles as well as its distinguishing features [23,27].

Recent human clinical trials have utilized various types of stem cell in the treatment of DM including: HSCs, MSCs, ESCs and UCB stem cells [1,3,28]. A meta-analysis on the utilization of stem cells in treating DM showed the following findings: (1) in selected patients, stem cell therapies are safe and effective therapeutic modalities provided they are used early in the disease course, (2) excellent outcome was achieved with CD34+ HSC therapies for type 1 DM, and (3) significantly higher benefit and superior outcome were obtained when using UCB-derived MSCs rather than BM-derived MSCs [3]. However, animal studies have suggested that MSCs, iPSCs and ESCs can differentiate into insulin-producing cells and their utilization can ultimately regulate insulin secretion [1,29]. Various stem cell therapies have the potential of providing promising and effective treatment for type 1 and possibly type 2 DM as shown by the decreased HbA1C and the increased C-peptide levels in animal studies as well as human clinical trials [1,29].

The efficacy of autologous HSCT for type 1 DM was first reported 11 years ago [30]. Subsequently, several studies have confirmed not only the safety but also the efficacy of this form of HSCT in types 1 and 2 of DM [28,29,31]. The combination of high-dose immunosuppressive therapy and HSC infusions has synergistic effects on: improvement of the immune regulatory networks, downregulation of the auto-reactive T-cells, renewal of the immune system, in addition to induction of insulin independence in type 1 DM [28,29,31,32]. Autologous HSCT in type 1 DM has shown the following results: increased C-peptide level, decreased HbA1C level, reconstitution of immune tolerance, preservation of islet β-cell function and variable durations of insulin independence that may extend up to 5 years [33-39]. Predictive factors for prolonged remission after autologous HSCT include: age, fasting C-peptide level and tumor necrosis factor a level [40]. However, candidates for autologous HSCT should be carefully selected as studies have shown that patients with the following characteristics are likely to benefit most from the procedure: young age, short interval between the diagnosis and HSCT, absence of diabetic ketoacidosis at presentation, absence of islet cell antibodies and having residual functioning β-cells [33,39,41]. Also, autologous HSCT using BM-mononuclear cells (MNCs) and PB-MNCs has been successfully performed in patients with type 2 DM [30,42,43]. A meta-analysis on autologous HSCT in type 2 DM that include 15 clinical trials and 497 patients has shown excellent glycemic control, increased insulin biosynthesis and increased insulin secretion from the existing β-cells thus autologous HSCT may prevent islet cell loss in type 2 DM [43].

Among adult stem cells, autologous MSCs have been used with variable degrees of success in studies on animal models as well as in human clinical trials [44]. More than 15 clinical trials using MSCs obtained from: PB, BM and UCB have been performed in the treatment of both types of DM and they resulted in: elevated C-peptide level, decreased HbA1C level and significant reduction in insulin requirements [45,46]. MSCs have also been used successfully in the treatment of diabetic foot and diabetic neuropathy [47,48]. MSC transplantation in types 1 and 2 DM has been shown to be safe and beneficial as demonstrated by clinical and preclinical trials [7]. Several iPSC lines have recently been derived from both diabetic patients and healthy individuals [9]. iPSCs derived from mouse models and humans can differentiate into β-like cells and may represent a novel approach for disease modeling and drug discovery [9,49,50].

The combination of stem cell therapies and ICT is a promising therapeutic approach that may ultimately become curative for type 1 DM [10,51,52]. In a diabetic mouse model, co-transplantation of BM-derived MSCs and islet cells resulted in tissue engraftment and β-cell...
survival thus providing graft protection, tissue revascularization and immune acceptance [53]. The combination of insulin-secreting AT-derived MSCs and BM-derived HSCs in 3 patients with insulin-dependent DM resulted in significant amelioration of their diabetic biochemical profiles for periods lasting for ≥ 27 months [54,55]. An open-label, phase I/phase II study using a technique called stem cell educator therapy showed the efficacy of human UCB-derived stem cells in simultaneously promoting islet β-cell regeneration and reversing autoimmune via systemic and local immunomodulation [56].

So, the era of cellular replacement therapy for DM has already started as the utilization of various types of stem cells to cure DM appears to be very promising [2,10]. However, despite being considered highly innovative therapeutic approaches, cellular therapies are still at experimental level and these treatments should be performed by highly experienced centers [2]. Our group has recently published the first world report of curing insulin dependent DM in a patient who received an autologous HSCT in order to control his multiple myeloma in March 2013 [57].

References


