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Clinical safety and therapeutic efficacy of autologous bone-marrow derived stem cells in restoring glycemic control and treating complications in diabetic patients.

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ABSTRACT

Diabetes is one of the most common chronic diseases worldwide, with around 537 million adults aged 20-79 living with the disease. It is a global epidemic and has a rapidly rising incidence. Traditional treatments for diabetes have limited efficacy in achieving long-term disease control. In recent years, the autologous infusion of bone marrow-derived mononuclear cells (BMMNC) has become a novel and effective therapeutic approach in treating autoimmune type 1 diabetes (T1DM). BMMNC contains two important types of stem cells, bone marrow-derived hematopoietic stem cells (BMHSC) and bone marrow-derived mesenchymal stem cells (BMMSC), which are currently used independently or coordinately in the treatment of T1DM. In this review, we summarize the clinical data concerning BMMNC, BMHSC, and BMMSC infusion in patients with diabetes (including type 1, type 2, and secondary diabetes) and diabetes-related complications. Research suggests that the autologous infusion of bone marrow stem cells is safe and effective, offering the potential to be widely used in patients with diabetes.

Keywords: Diabetes, Bone Marrow, Autologous Transplantation, Hematopoietic Stem Cell, Mesenchymal Stem Cell, Bone Marrow-Derived Mononuclear Cells.

Introduction

Diabetes is one of the most common chronic diseases worldwide, with around 537 million adults aged 20-79 living with the disease 1. Diabetes mellitus, which includes type 1 (T1DM) and type 2 (T2DM), leads to high morbidity and mortality, and as a result, presents a huge global burden. According to the CDC (Centers for Disease Control and Prevention) 2, there are at least 37.3 million Americans (11.3% of the population) living with diabetes, and another 38% of US adult population have prediabetes. In 2017, the cost of diagnosed diabetes in the US was estimated at $327 billion 3. Traditional therapeutic diabetes strategies such as diet control, exercise, insulin treatment, and medications do not have satisfactory sustained outcomes long-term. Pancreatic and islet transplantation has been considered for T1DM and bariatric surgery has exceptional effects on refractory T2DM, but these applications have been limited thus far 4,5. Furthermore, both have potential surgery-related risks and long-term complications associated with chronic immune suppression.

In recent years, the use of bone marrow-derived mononuclear (BMMNC) cells have shown to be a promising therapeutic strategy for diabetes and some other diseases 6. BMMNCs contain two main types of bone marrow stem cells, i.e., bone marrow -derived hematopoietic stem cells (BMHSCs) and bone marrow-derived mesenchymal stem cells (BMMSCs) 6,7,8. Widely located in the bone marrow, BMHSCs play a key role in producing all types of blood cells. BMMSCs occur in the bone marrow stromal compartment. These cells mechanically support the hematopoietic microenvironment, and additionally have the capacity to differentiate into a variety of cell types such as neuronal cells, cardiomyocyte, lung epithelial cells, and pancreatic beta cells 9. A systematic review 8 compared different types of stem cells and concluded that the T1DM therapy by BMHSC infusion, and transplantation of BMMNCs combined with mesenchymal stem cells for T2DM, presented promising therapies.

Stem cell transplants can be allogeneic or autologous, depending on the source of the cells. Compared to allogeneic transplantation, autologous infusion of bone marrow stem cells is widely accepted as it reduces the graft versus host disease and engraftment syndrome 10,11. In this review, we summarize the recent clinical data of autologous BMMNC infusion in the treatment of diabetes. To our knowledge, this is the first review paper on this topic.

Autologous infusion of BMMNC in T1DM

T1DM, formerly known as insulin-dependent or juvenile diabetes, is caused by an autoimmune process of islet beta-cell destruction that results in insulin deficiency and hyperglycemia. Compared to pancreatic transplantation, stem cell transplantation has fewer limitations and has wider applications due its accessibility. The cells, such as BMMNCs, can be obtained with relative ease from the individual. BMMNCs can be infused through veins, arteries, or directly into tissues. Jawale 12 harvested 7.86 x 107 bone marrow stem cells and divided these into thirds: one third of the isolated cells were delivered into the omental pouch, another one third was delivered into peritoneal cavity, and the remaining third was given intravenously. This method was reported to be safe and effective for the long-term treatment of T1DM.

Cai et al. 13 conducted a pilot randomized controlled trial (RCT) in patients with T1DM. At 1

year after a co-transplantation of autologous BMMNCs plus umbilical cord mesenchymal stem cells through the pancreatic artery, patients showed moderate improvement of metabolic measures such as the levels of endogenous C-peptide, insulin, glucose, and hemoglobin A1C (HbA1c) compared to controls. Mesples et al. 14 treated 2 patients with recently diagnosed T1DM by infusing BMMNCs into the liver via an ultrasound guided needle. The follow up at 12 months after treatment exhibited negative values in anti-pancreatic islets cells antibodies (ICAs), glutamic acid decarboxylase (GAD) antibodies, and anti-insulin antibodies, with increased C-peptides and decreased glycemic levels 14. In addition, the anti-T1DM effects of BMMNC can be further improved by the addition of exercise in combination with the autologous BMMNC transplantation, which showed better glycemic control than stem cell alone in patients with T1DM 15.

The combined transplantation of mesenchymal and hematopoietic stem cells has been used in treatments of diseases 9 including T1DM. The combination of BMHSCs and other types of mesenchymal stem cells have been addressed in T1DM treatment. Thakkar et al. 16 performed a prospective trial for patients with T1DM and found that autologous BMHSCs plus adipose-derived insulin-secreting mesenchymal stromal cells offered satisfactory long-term hyperglycemic control. The co-infusion of BMMSC and other types of hematopoietic stem cells has not been studied and needs to be explored further in research studies.

As an important type of BMMNC, BMHSC therapy has also been used as stand-alone treatment for autoimmune diseases including T1DM 17. The rationale of this therapy is that BMHSC is likely to influence immunity and correct immune aberration 17,18. Voltarelli et al. 19 studied 15 patients with T1DM diagnosed within the previous 6 weeks. At 36 months following intravenous (IV) BMHSC infusion, 14 patients no longer required insulin and showed significantly improved glycemic control, with mild and acceptable adverse effects. Snarski et al. 20 reached the same conclusion in a study of 8 patients with newly diagnosed T1DM after performing BMHSC transplantation. Following transplantation, all patients were less dependent on exogenous insulin and exhibited lower HbA1c levels. Li et al. 21 did BMHSC transplantation in patients with T1DM who developed symptoms within 12 months of diagnosis. In 31-54 months, 11 out of 15 patients had decreased HbA1c and increased C-peptide concentrations, along with reduced doses of insulin for glycemic control, indicating an improvement of beta-cell function. A follow-up study by Couri et al also exhibited an increase in C-peptide and a reduction in insulin consumption 22.

With the ability to differentiate into islet cells and modulate the microenvironment, BMMSC therapy is also used stand-alone in T1DM treatment, although the reports of using BMMCS alone are fewer compared to using BMHSC alone. In a RCT 23, an IV injection of autologous BMMSC or placebo was performed in 21 patients with newly diagnosed T1DM. The results indicated that patients who underwent BMMSC treatment showed improved levels of C-peptide and HbA1c. Interestingly, BMMSC shifted pro-inflammatory cytokines into anti-inflammatory markers 23. Similarly, a study by Carlsson et al. 24 demonstrated positive outcomes. In the study, patients with new-onset T1DM were given IV autologous BMMSC treatment and followed up for 1 year. Compared to the control group, their beta-cell functions were

preserved 24.

Building on the above evidence base for the use of BMMNCs as a promising therapeutic strategy for diabetes, our team recently reported a novel approach for BMMNC collection using a cohort of 6 young diabetic patients 25. After using Filgrastim for 4 days, bone marrow was aspirated on day 5 and stem cells were extracted from the anterior superior iliac spine, which was followed by an IV injection. The qualified autologous bone marrow stem cells were collected and identified as mononuclear cells >180×106 /kg and CD34+ cells >0.22%. These patients had a diagnosis of T1DM for <120 days (60-120 days) and were aged 12 years old on average. At 6 months after stem cell transplantation, 5 patients demonstrated decreased blood glucose and HbA1C levels along with improved values of ICA, GAD, and tyrosine phosphatase-related islet antigen 2 antibodies 25. In this study, BMHSC was stimulated and BMMSC was not stimulated.

Autologous infusion of BMMNCs in T2DM

T2DM, previously called non-insulin-dependent or adult-onset diabetes, is characterized by a combination of insulin resistance and islet beta-cell dysfunction. It accounts for over 90% of the caseload of diagnosed diabetes. A meta-analysis 26 showed that BMMNC therapy for T2DM resulted in improved glycemic control, insulin secretion and biosynthesis in patients, and suggested that it might prevent the loss of islet cells. Bhansali et al. 27,28 found that BMMNC transplantation led to a reduction in the required insulin dose and an improvement in C-peptide response in patients with T2DM, although insulin sensitivity remained unchanged. Hu et al. conducted a 3-year data that indicated similar improvements 29.

The approach of infusing stem cells in T2DM varies from that used in T1DM. Sood et al. 30 divided patients with T2DM into different groups by using different transplantation routes for BMMCs. In this study, 7 patients received BMMNC in the superior pancreaticoduodenal artery under fluoroscopic guidance, an additional 7 patients received the infusion in the splenic artery, and the final 7 patients received the peripheral IV route. At 6-months post-treatment, the patients who underwent BMMNC infusion through the artery had significantly decreased insulin dose requirements while those who received transplantation via IV did not have any effects 30. This indicates that the IV route is as optimal for T2DM therapy, unlike T1DM therapy. Besides the superior pancreaticoduodenal artery and splenic artery, other arteries have been utilized to deliver BMMNC for T2DM therapy. Wehbe et al. 7 conducted a study in which 6 patients with T2DM underwent autologous infusion of BMMCs into the celiac and superior mesenteric arteries. Five patients showed normalization of fasting glucose and HbA1C with a concomitant reduction of medication required. Infusion through the great pancreatic artery has been shown to be safe and effective 31.

The effectiveness of the intrapancreatic autologous stem cell may be enhanced by a combination with hyperbaric oxygen treatment. Estrada et al. studied 48 patients with T2DM 32,33. In 1-year follow-up after the combined treatments, the patients exhibited increased metabolic control and reduced insulin requirements compared to either the standard treatment or baseline groups. However, this conclusion contrasted with Wu et al.'s study 34, which found BMMNC infusion to be a good therapeutic strategy for T2DM. According to this research, the effect of hyperbaric oxygen treatment combined with

BMMNCs is comparable to BMMNCs alone (with no significant difference), as the addition of hyperbaric oxygen treatment was not shown to strengthen the effect of BMMNCs 34. More research is needed to understand these mechanisms and for further analysis.

BMMSCs can be used as a stand-alone therapy in patients with T2DM and has demonstrated good results. There are no reports using autologous BMHSC therapy in patients with T2DM, however the use of BMMSC therapy has demonstrated satisfactory outcomes 35. Bhansali et al. 35 randomly assigned patients with T2DM into groups receiving either BMMNCs or BMMSCs via superior pancreaticoduodenal arterial injection. At 12 months after treatment, both groups showed a reduction in HbA1C level and insulin requirements, and BMMSC infusion was shown to increase insulin sensitivity and the C-peptide response.

Autologous infusion of BMMNC in other types of diabetes

Other types of diabetes exist, such as gestational diabetes and secondary diabetes. To date, BMMNC infusion has not been used in the treatment of gestational diabetes, although it has been applied in the prevention of pancreatogenic diabetes (also called type 3C diabetes 36). In a pilot study by Wang et al. 37, autologous BMMSC was infused via portal vein along with the islet transplantation to patients with chronic pancreatitis. Compared to control data, these patients required lower doses of insulin and had lower levels of blood glucose. Thakkar et al. 38 reported a successful case of treatment for a patient with pancreatogenic diabetes using stem cells. In this case, BMHSCs were implanted along with adipose tissue derived insulin-secreting mesenchymal stem-cells into subcutaneous tissue, portal and thymic circulation. Compared to baseline, the patient maintained better blood sugar (postprandial blood sugar from 389 mg/dl to 165 mg/dl) and HbA1C (from 8.9% to 6.8%) results with less insulin consumption (from 72 IU/day to 36 IU/day) at the 27-month follow-up 38.

Autologous infusion of BMMNC in diabetic complications

In addition to hyperglycemic control, BMMNCs plays a role in alleviating diabetic complications. In a study by Wu et al., results from 8-year follow up after the co-transplantation of autologous BMMNCs and umbilical cord mesenchymal stem cells showed that this was associated with a reduced incidence of T1DM chronic complications 39. Similarly, Gaipov et al. revealed that the infusion of autologous BMMNCs improved nephropathy in patients with T1DM 40. A phase I trial showed that intravitreal injection of autologous BMMNCs inhibited the progression of hereditary retinal dystrophy 41.

BMMSC therapy is emerging as a promising, safe, and effective treatment method for diabetic complications. clinical research has indicated that BMMNCs relieved diabetic (both T1DM and T2DM) disease complications such as foot ulcers and critical limb ischemia 42,43,44,45. According to a study by Gu et al.'s 46, a single IV infusion of autologous BMMSCs in patients with non-proliferative diabetic retinopathy improved visual acuity and central macular and subfield thickness, with decreased fasting blood glucose and hypersensitive C-reactive protein levels. A study by Demour et al. 47 found that intracavernous autologous BMMSCs were a safe and effective for treatment of diabetic patients with erectile dysfunction.

Similarly, studies by Dash et al. 48 and Lu et al. 49 demonstrated that the topical application of BMMSCs in patients with chronic diabetic foot ulcers resulted in improvements in terms of increased pain-free walking distance, reduction in wound size and decreased ulcer recurrence rate, and additionally, promoted blood flow. The role of BMMSCs in curing critical limb ischemia 49,50 and recurrent lower limb bullosis diabeticorum 51 in patients with T2DM was also reported. It is important to note that the autologous bone marrow stem cell transplantation may have side effects. For example, it was reported that the function of BMMSCs might be compromised with a long-term exposure to chronic inflammation 52 or reduced due to a long history of T2DM and obesity 53, however these side effects need to be confirmed and further explored in future research.

Conclusion

BMMNCs and its components of BMHSCs and BMMSCs have the capacity to treat diabetes and diabetes-related complications. Several studies have been performed and different approaches have been explored. Preliminary research has shown that autologous infusion of bone marrow stem cells is feasible, safe, and effective. In the future, rigorous RCT data using larger groups and longer-term follow-up, with more comparisons between studies may be needed to standardize and optimize autologous bone marrow stem cell infusion therapies for diabetes and other diseases.

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