International Journal of Pharmaceutics 543 (2018) 107–120

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Review

Current advanced therapy cell-based medicinal products for type-1-diabetes treatment

Alberto Cañibano-Hernández[a,b], Laura Sáenz del Burgo[a,b], Albert Espona-Noguera[a,b], Jesús Ciriza[a,b,*], Jose Luis Pedraz[a,b,*]

[a] NanoBioCel Group, Laboratory of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of the Basque Country UPV/EHU, Vitoria-Gasteiz 01006, Spain

[b] Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine, CIBER-BBN, Spain

ARTICLE INFO

Keywords:
Type I diabetes
Insulin
Advanced therapy medicinal products
Cell replenishment
Stem cells

ABSTRACT

In the XXI century diabetes mellitus has become one of the main threats to human health with higher incidence in regions such as Europe and North America. Type 1 diabetes mellitus (T1DM) occurs as a consequence of the immune-mediated destruction of insulin producing β-cells located in the endocrine part of the pancreas, the islets of Langerhans. The administration of exogenous insulin through daily injections is the most prominent treatment for T1DM but its administration is frequently associated to failure in glucose metabolism control, finally leading to hyperglycemia episodes. Other approaches have been developed in the past decades, such as whole pancreas and islet allotransplantation, but they are restricted to patients who exhibit frequent episodes of hypoglycemia or renal failure because the lack of donors and islet survival. Moreover, patients transplanted with either whole pancreas or islets require of immune suppression to avoid the rejection of the transplant. Currently, advanced therapy medicinal products (ATMP), such as implantable devices, have been developed in order to reduce immune rejection response while increasing cell survival. To overcome these issues, ATMPs must promote vascularization, guaranteeing the nutritional contribution, while providing O_2 until vasculature can surround the device. Moreover, it should help in the immune-protection to avoid acute and chronic rejection. The transplanted cells or islets should be embedded within biomaterials with tunable properties like injectability, stiffness and porosity mimicking natural ECM structural characteristics. And finally, an infinitive cell source that solves the donor scarcity should be found such as insulin producing cells derived from mesenchymal stem cells (MSCs), embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). Several companies have registered their ATMPs and future studies envision new prototypes. In this review, we will discuss the mechanisms and etiology of diabetes, comparing the clinical trials in the last decades in order to define the main characteristics for future ATMPs.

1. Introduction

Nearly 350 million people worldwide are affected by Diabetes mellitus (DM), a chronic disease that has become as one of the major diseases in the XXI century. Diabetes is classified by the American Diabetes Association as type I diabetes mellitus (T1DM), type II diabetes mellitus (T2DM), gestational diabetes mellitus (GDM) and other minor types grouped as type III diabetes mellitus. Type 1 diabetes mellitus (T1DM), where we will focus on this review, is characterized by an autoimmune destruction of pancreatic β-cells resulting in severe insulin deficiency, after an asymptomatic period over years. It develops mostly in young people accounting for 5–10% of the diabetic subjects (Yoon and Jun, 2005). T1DM patients have shown that β-cells from the islets of Langerhans are destroyed by infiltration of dendritic cells (DCs), macrophages and T lymphocytes (both CD4+ and CD8+). Immune reaction is specific against insulin-producing β-cells, not affecting other cells in the islets of Langerhans, such as α-cells (glucagon producing cells) or δ-cells (somatostatin producing cells) (Richardson et al., 2014). Type II diabetes mellitus is also known as insulin independent diabetes because patients present insulin resistance and deficiency, without need of insulin treatment to survive. The specific etiology of T2DM is not completely clarified and there are probably different causes, including obesity and genetic predisposition (Diagnosis and classification of diabetes mellitus, 2010). Gestational

* Corresponding authors at: NanoBioCel Group, Laboratory of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of the Basque Country UPV/EHU, Paseo de la Universidad, 7, 01006 Vitoria-Gasteiz, Spain.
E-mail addresses: jciriza@ciber-bbn.es (J. Ciriza), joseluis.pedraz@ehu.eus (J.L. Pedraz).

https://doi.org/10.1016/j.ijpharm.2018.03.041
Received 25 January 2018; Received in revised form 19 March 2018; Accepted 24 March 2018
Available online 27 March 2018
0378-5173/

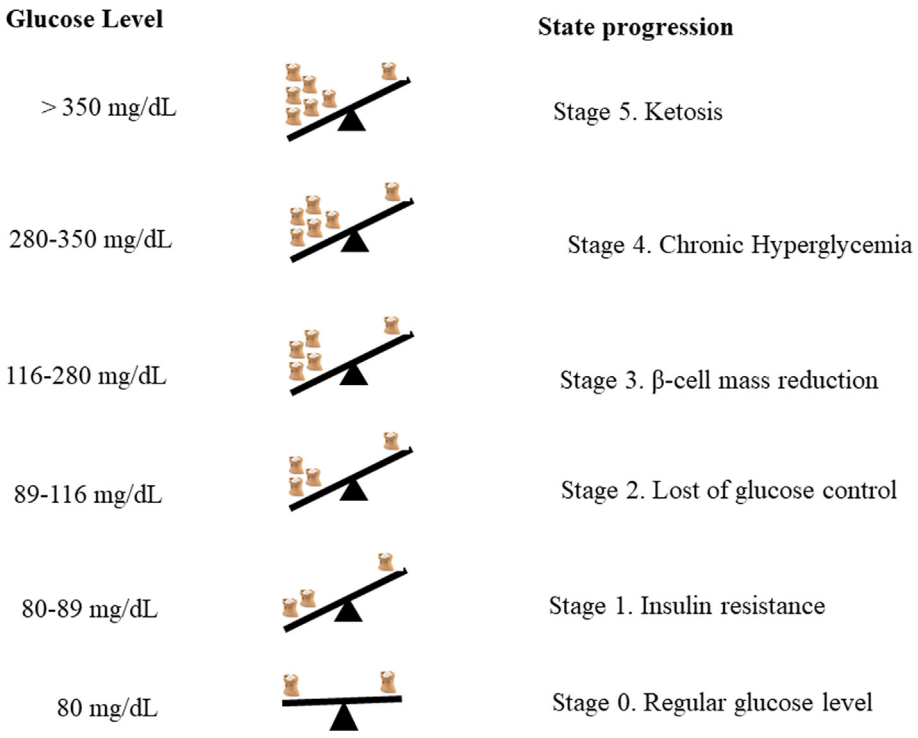

Fig. 1. Five stages of progression of diabetes.

diabetes mellitus can be defined as a deficiency in glucose metabolism control identified during pregnancy, which normally is reverted post-partum (Kim, 2014).

To define diabetes, it is necessary to analyze the progression of symptoms in the disease. Attending to changes in the cells mass, phenotype and cell functionality five stages can be defined in the progression of diabetes (Knowler et al., 2002) (Fig. 1). The regular stage of β-cells corresponds to blood glucose levels of 4.5 mmol/l (80 mg/dl) while the first stage of diabetes is characterized by an insulin secretion increase to maintain the regular glucose levels, because of insulin resistance caused by obesity, physical inactivity and genetic predisposition. During this stage, it has been described an increase of β-cell mass, probably due to an increase of β-cell number and β-cell hypertrophy (Livingstone et al., 2015). In stage 2, the blood glucose levels overcome 5.0–6.5 mmol/l (89–116 mg/dl) and, normal glucose levels from stage 0 cannot be longer maintained. Despite of people in stage 2 usually evade progression to type II diabetes for years by adhering to a diet and exercise regimen (Miao et al., 2007), people with T1DM experience a fast increase of β-cell mass destruction. Next, T1DM evolves to a decompensated stage 3, when glucose levels rise rapidly over 7.3 mmol/l (130 mg/dl), probably determined by glucose toxicity effects on β-cells, leading to β-cell mass reduction and less efficient insulin secretion (Felig, 1984). In stage 4, the increment of β-cells destruction displays blood glucose values higher than 15 mmol (280 mg/dl) which induces a progression to ketoacidosis. This stage lasts mostly the lifetime of T2DM patients, while the rapid progressive autoimmune destruction of β-cells inT1DM, often leads to stage 5 relatively quickly (Giaccari et al., 2009). In the stage 5, there is a fast β-cell mass reduction enhancing the glucose levels up to 22 mmol/l (350 mg/dl). At this stage, the progression to ketosis and insulin dependence is unavoidable. Once β-cell destruction is completed at stage 5, there is no possible to return across the stages. Stage 5 is common in T1DM, while rarely occurs in T2DM.

The treatment of T1DM usually depends on the stage of progression. The ideal goal of a future treatment for T1DM would be to reverse the β-cell destruction, restore the glucose metabolic control and prevent the onset and progression of autoimmunity. The most prominent treatment is the insulin replacement by exogenous administration through daily injections or an insulin pump. To avoid the issues related with insulin daily injections, other research groups have focused on healing T1DM with β-pancreatic cell replenishment, either by whole vascularized pancreas transplantation or by islet transplantation. However, whole pancreas transplantation requires complex surgical techniques and immunosuppression for life. Currently, pancreatic islets transplantation represents the best option for T1DM cure, even with limitations such as donor scarcity, requiring new administration routes.

2. Characteristics of an optimal advanced therapy medicinal product

Nowadays, new technologies are investigated to heal T1DM, trying to overcome those failures of T1DM classical treatments. The advanced therapy medicinal products (ATMP) are one of these technologies applied to diabetes treatment which, can be defined as a combination of a wide variety of medicines or therapeutic products in a complex device. ATMPs consist of Cell-Based Medicinal Products (CBMPs) and Gene Therapy Medicinal Products (GTMPs) but, in this review, we will focus in the application of CBMPs to T1DM treatment. ATMPs containing cells growing inside should gather some characteristics for cell survival. The regular oxygen and nutrient supply, as well as the ability of device to generate its own vascular network, are very important for cell survival in the ATMP. Besides, the device needs to avoid immune rejection by biocompatible materials protection. Also, it would be desirable the possibility of injecting the embedded cell without the need of surgery. Cell sources enclosed inside the ATMP are other characteristic to be tuned, being preferred solutions based in the incorporation of new cell sources to solve the problem of donor scarcity of pancreatic islets. Finally, the ATMPs should be subjected to a series of safety and quality regulations. We will focus in the minimal characteristics gathered by the ideal advanced therapy medicinal product applied to diabetes treatment (Fig. 2).

2.1. Oxygen supply

Pancreatic cells are highly oxygen dependent, consuming