Human Hematopoietic Stem/Progenitor Cells in T1DM Treatment

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Type 1 diabetes mellitus (T1DM) is a highly prevalent autoimmune disease causing the destruction of pancreatic islet β-cells. The resulting insulin production deficiency leads to a lifelong need for insulin re-placement therapy, systemic complications, and reduced life quality and expectancy. Cell therapy has been extensively attempted to restore insulin independence (IID), and autologous nonmyeloablative hematopoietic stem cell transplantation (AHST) has appeared to give the most promising results.

T1DM diabetes CD34 HSPCs cell therapy

1. Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disease affecting pancreatic islets and, in particular, β-cells, which are responsible for insulin production [1][2]. Data from a metanalysis performed in 2020 showed a worldwide incidence of 15 per 100,000 people and a prevalence of 9.5%, with a constantly increasing trend [3]. Moreover, T1DM has been found to account for 5.6% of diabetes cases in an American National Health Interview Survey [4]. Its incidence rate peaks at 10–14 years, and only one quarter of cases are diagnosed in adults [5]. Complications are mostly driven by hyperglycaemia and include microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (cardiovascular disease, cerebrovascular accidents, peripheral vascular disease) damage. However, unlike type 2 diabetes mellitus (T2DM), T1DM complications can extend beyond the common effects of hyperglycaemia: for example, cardiac autoimmunity and cardiac autoantibodies have been found to be associated with poor glycaemic control in T1DM but not in T2DM, with a pathogenetic model more similar to Chagas cardiomyopathy [6]. On the other hand, hyperglycaemia in T2DM is due to a combined mechanism of insulin resistance and insulin production exhaustion; T2DM tends to onset at an older age and is usually associated with other cardiovascular risk factors including obesity, hypertension, dyslipidaemia and physical inactivity [7]. Nevertheless, observational studies comparing T1DM and T2DM suggest that T2DM, when similar to T1DM in terms of control and age of onset, is associated with an overall higher number of complications, especially microvascular and cardiovascular [8][9].

T1DM patients have been found to have a life expectancy at birth of 68.6 years, which was 12.2 years less than in the general population in an Australian cohort [10]. Insulin replacement therapy is the cornerstone treatment for T1DM, but it requires multiple daily injections and glycaemia measurements, with careful planning of time and composition of meals, and a significant detrimental effect on the quality of life [11]. Once β-cells are lost, no oral drug can compensate for insulin production deficiency. Therefore, many efforts have been made to find a curative

option: several trials involving the administration of anti-inflammatory drugs have been designed, with the aim of stopping and hopefully reverting the β-cell destruction process, but without substantial success [12]. Pancreatic islet transplantation has been tested, but it requires a surgical procedure and lifelong immunosuppression, and usually T1DM relapses soon due to the destruction of the transplanted islets [13].

2. Hematopoietic Stem/Progenitor Cells for Cell Therapy

HSPCs are self-renewing and multipotent cells that reside in specialized niches within the bone marrow. Identified by the CD34 surface antigen, whose function is still unknown, they are capable of differentiating in all types of blood cells, both of myeloid and lymphoid lineage, and to reconstitute the whole hematopoietic system after bone marrow ablation [14][15]. A small number of $CD34^+$ cells can also be found in the peripheral blood (~3 cells/μL), from which they move throughout the body [16]. The physiological significance of their migration seems to correlate with the patrolling of peripheral organs, in which they maintain tissue homeostasis and regeneration, and immune responsiveness [17]. The CD34 marker, although routinely used to identify and isolate human HSPCs, is also expressed by a broader group of cell populations, including multipotent mesenchymal stem/stromal cells (MSCs), vascular endothelial progenitor cells and epithelial progenitor cells [18][19][20][21]. The isolation of $CD34^+$ cells from peripheral or bone marrow blood yields a mixture of cells characterized by different states of differentiation, including cells with vasculotrophic function, namely endothelial progenitor cells (EPCs). The discovery of this cell population, initially identified by double positivity for CD34 and KDR markers, by Asahara at the end of the 1990s pioneered over 20 years of research in stem cell biology and regenerative medicine [22]. Since then, numerous studies have attempted to characterize EPC origin and phenotype. As reviewed in more detail elsewhere [17][23][24], two different approaches have been used so far: one aiming at the identification of circulating EPCs by flow cytometric assay of peripheral blood samples, and the other based on cell culture methods. This latter led to the identification of early EPCs ($CD45^+$, $CD14^+$ $CD31^+$ $CD34^-$ $CD146^-$) and late EPCs ($CD31^+$, $CD146^+$, $CD105^+$, $CD45^-$, $CD14^-$), whose effective existence and function in vivo are elusive. Overall, both approaches led to controversial results and a general lack of consensus. Today, due to the impossibility of physically separating EPCs from HSPCs for their overlapping phenotype, scientists are inclined to identify circulating EPCs with the more generic $CD34^+$/$CD133^+$ HSPC population because they are ancestors of EPC [23][25]. In this regard, $CD34^+$ cells as a whole are known to possess vascular regeneration capacity and proangiogenic potential, and their circulating level reduction is linked to poorer outcomes in cardiovascular diseases, in chronic haemodialysis patients and after cerebral infarction [16][26][27][28]. Nevertheless, most of the preclinical and clinical studies so far reported were performed in view of the putative cardiovascular protective and pro-angiogenic role of HSPCs, overlooking that these cells are precursors of immune system cells and that possess an immunoregulatory function. Consistently, allogeneic bone marrow HSPCs transplantation in non-obese diabetic (NOD) mice has been shown to prevent diabetes onset and to restore insulin independence (IID) in type 1 diabetic mice, despite not being able to regenerate lost pancreatic islets. Such evidence, together with the fact that transplanted islets from the same allogeneic donor could be accepted by diabetic recipients previously transplanted with bone marrow and transiently restore IID, suggested that the main mechanism of action of HSPCs lies in their immunomodulatory properties rather than a mere regenerative effect. This hypothesis was further supported by clinical evidence that $CD34^+$ cells

exhibited immune system resetting and reconstitution properties after autologous nonmyeloablative (as opposed to standard peripheral blood stem cell transplantation, which generally implies bone marrow ablation of the host [29]) hematopoietic stem cell transplantation (AHST): in multiple sclerosis studies, AHST determined an increase in thymus-derived naive T cells, a decrease in central-memory T cells, the recovery of a different T-cell receptor repertoire and immune system drifting towards a more tolerant phenotype [30][31]. Similar evidence of the immunotolerant properties of HSPCs was found when assessed for the treatment of systemic lupus erythematosus [32].

Besides $CD34^+$ HSPCs, other cell types have been tested in trials for the treatment of T1DM. These include the unselected bone marrow-derived mononuclear cell (BM-MNC) fraction and mesenchymal stem cells (MSCs). The former consists of a pool of different kinds of cells, typically obtained by bone marrow aspiration from the iliac crest, in which $CD34^+$ cells represent a fraction of about 0.5–6% and are most likely responsible for the therapeutic effect [33][34]. On the other hand, MSCs are multipotent cells that can differentiate in several cell types, such as osteoblasts, chondroblasts, myocytes, adipocytes and β-cell-like cells [17][35][36][37]; can be collected from various tissues, including bone marrow, fat and umbilical cord blood; and possess immunomodulatory properties and the potential to protect pancreatic islets and promote their regeneration [38][39][40].

One last cell type, i.e., embryonic stem cells (ESCs), is under evaluation in some clinical trials (NCT02239354, NCT04678557, NCT03163511, NCT05210530, NCT04786262). Unlike other cell types, these are manipulated to obtain pancreatic endodermal cells that can be administered to patients to restore insulin production directly [41]. Furthermore, studies with immunodeficient mice have shown their capability to correctly differentiate to stem cell-derived β-like cells and become insulin-sensitive when transplanted [42]. Being allogeneic by definition, they require host immunosuppression, to be engineered to evade immune response, or to be encapsulated in subcutaneous immunoisolation devices [43]. Another downside of these cells is that they are not available worldwide due to ethical concerns. Attempts have been made to reproduce them with patient-derived induced pluripotent stem cells (IPSCs), which have proved a useful model for research but are still unsuitable for therapeutic use due to potential instability [44].

3. Hematopoietic Stem/Progenitor Cells in Clinical Trials

3.1. Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation

The usefulness of HSPCs for the treatment of T1DM has been evaluated in several clinical trials employing the AHST approach. Since T1DM is an autoimmune disease characterized by autoreactivity against pancreatic islet β-cells, with consequent impaired insulin production [2], the researchers aimed to verify if AHST could interrupt or at least decelerate the β-cell destruction by the immune system in a setting of new-onset/early T1DM, with benefits in terms of independence from insulin administration or a reduction in dose [31]. This approach had the potential to prove a more effective, less risky and expensive, and lifelong immunosuppression-free curative alternative to pancreatic islet transplantation [13].

The typical protocol design was rather consistent among the different clinical trials. Generally, it included a stem cell mobilization phase with cyclophosphamide and granulocyte colony-stimulating factor (GCSF), and consequent leukapheresis with a continuous-flow blood cell separator for the isolation of $CD34^+$ cells, followed by a conditioning (immune ablative) phase with cyclophosphamide and antithymocyte globulin. At the end of the conditioning treatment, the patients underwent stem cell infusion and antimicrobial prophylaxis in an isolated environment. All protocols were approved by local regulatory authorities/ethical committees.

3.2. The Brazilian Study

The first study was conducted by Voltarelli et al. in Brazil (NCT00315133). They enrolled 15 patients, including Black, White, and mixed races with T1DM diagnosed within the previous 6 weeks between November 2003 and July 2006, with a follow-up of 7 to 36 months. Stem cells were mobilized with cyclophosphamide and GCSF; afterwards, the patients underwent leukapheresis, and the cells were frozen in 10% dimethyl sulfoxide in a rate-controlled freezer and stored in the vapor phase of liquid nitrogen. The conditioning phase consisted of a 5-day treatment with cyclophosphamide and rabbit antithymocyte globulin; prophylaxis of the antithymocyte globulin reactions was performed with dexchlorpheniramine, except for patient n°1 (treated with corticosteroids due to diabetic ketoacidosis = DKA). After conditioning, stem cell infusion (at least 3×10^6/kg) was delivered, followed by GCSF administration after 5 days. The patients were isolated in rooms equipped with high-efficiency particulate air filters and received antimicrobial prophylaxis. Exclusion criteria were positive serology for human immunodeficiency virus, hepatitis B or C, pregnancy and underlying hematologic, nephrological, cardiac, psychiatric, or hepatic disease and DKA (see below).

The study gave very promising results: all patients except for n°1 (diagnosed with DKA) achieved IID at a certain point of the follow-up (which lasted for a median of 14.8 months and a maximum of 35 months); thus, thereafter, DKA was listed among the exclusion criteria. Thirteen patients became continuously IID and one resumed insulin treatment 1 year after ASHT. Moreover, the mean area under the curve (AUC) of C-peptide levels before transplantation (92.0 ng/mL per 2 h) showed a statistically significant increase at 6 months, 12 and 24 months; anti-glutamic acid decarboxylase antibody (GADA) levels were significantly lower after 6 months; at the beginning of the study, 11 of 14 patients presented glycated haemoglobin (HbA1c) values above 7%, but in 3 months a persistent drop was observed except for one patient, who eventually relapsed [31].

After ASHT, mild side effects were observed in most patients (such as febrile neutropenia, nausea, vomiting, alopecia), plus a case of bilateral pneumonia that required supplementary oxygen therapy and responded completely to broad-spectrum antibiotics. Further, during follow-up, there was a case of autoimmune hypothyroidism and transient renal dysfunction associated with rhabdomyolysis and a case of mild hypergonadotropic hypogonadism. No mortality was associated with the treatment.

This study provided the first clinical evidence of sustained recovery of IID in T1DM patients after treatment with AHST. Two years later, the same group published the results of the extended follow-up with the addition of 8 new patients, for a total of 23 [45]. After a follow-up of 7–58 months, 12 had become continuously IID and 8 only

transiently, among which 4 resumed insulin after an upper respiratory tract infection; interestingly, two patients recovered IID after the addition of the dipeptidyl peptidase 4 inhibitor sitagliptin, with the restoration of β-cell function witnessed by the upturn of C-peptide levels. The authors suggested that the beneficial effects of sitagliptin could be due to the rapid suppression of glucagon levels in parallel with further increase in insulin production, together with a potential immunoregulatory function in autoimmune insulitis [45][46]. Unfortunately, the combination of AHST and sitagliptin has not been further tested in other studies. Only three patients never became IID, two of which developed DKA and two underwent corticosteroid treatment. HbA1c levels in continuously IID patients constantly remained under 7% and AUC of C-peptide levels increased significantly in all patients with at least transient IID. Concerning adverse reactions, an additional patient developed bilateral nosocomial pneumonia that effectively responded to intravenous broad-spectrum antibiotics, three patients developed late endocrine dysfunction (autoimmune hypothyroidism, Graves' disease and transient hypergonadotropic hypogonadism), and nine patients developed oligospermia. No mortality was documented [45].

In summary, Voltarelli et al. confirmed that AHST was capable of reversing T1DM in humans, at least for up 4 years and with an acceptable burden of adverse effects.

3.3. The Polish Study

A subsequent study was performed by Snarsky et al. in Poland, initially on a small cohort of 8 patients [47]. The Brazilian study protocol was modified by implementing 2–3 preliminary plasmapheresis sessions to remove circulating antibodies and immunological complexes, based on the observation that plasmapheresis can change the clinical course of diabetes [48]. All patients became IID after AHST, and only one resumed insulin treatment later; 6 patients were given acarbose additionally to improve glycaemic control. After AHST, HbA1c mean levels significantly dropped, and C-peptide levels rose. There were no major complications and some mild adverse effects such as nausea and fever [47].

The cohort of patients was later expanded to 24 participants: 20 remained insulin-free for at least 9.5 months, and 4 of them were still IID at the end of follow-up (up to 80 months). Unfortunately, 4 patients developed important antithymocyte globulin-related skin reaction/vasculitis, 1 patient developed pulmonary emphysema after the insertion of a central venous catheter and one patient died from *Pseudomonas Aeruginosa* sepsis [49].

3.4. The Chinese Studies

Two different Chinese clinical trials have been officially registered (NCT01341899 and NCT00807651), involving patients recruited in Shanghai and Nanjing; however, multiple papers have been published by the authors, presenting the outcomes of different pools of patients with sometimes very similar baseline characteristics. For this reason, a clear assessment of their overall findings is difficult to perform.

Li et al. recruited 13 Chinese patients and designed a protocol similar to the Brazilian one [50]. Only 3 patients developed IID, 1 of which relapsed after 7 months; 8 patients simply required reduced insulin doses for adequate glycaemic control and 2 patients were non-responders. The reason for a lower IID rate compared to the previous

studies was ascribed to an average longer time from T1DM onset (up to 12 months), a more aggressive disease (10 patients experienced DKA, although among them were two of the three patients who achieved IID) and stronger immunity (more than 50% of patients developed autoantibodies against two β-cell antigens before AHST). Nevertheless, the levels of serum fasting and post-prandial C-peptide in responding patients for at least 6 months after AHST were significantly higher than before treatment, while plasma HbA1c levels were significantly lower. Only mild side effects were documented, plus a case of autoimmune thyroiditis 6 months after AHST. The researchers also characterized the immunological state of the patients after AHST and found out that only $CD4^+$ T lymphocytes, unlike other cells, remained persistently lower after immune reconstitution; the concentrations of serum IL-1, IL-17 and TNF-α at 3 months and TNF-α and TGF-β at 6 months after AHST were significantly lower than before treatment, while TGF-β levels raised at 36 months. Moreover, the number of infused $CD34^+$ cells was positively correlated with the concentrations of serum IL-10, IL-4 and TGF-β but negatively with TNF-α (despite IL-10 and IL-4 levels remaining globally unchanged over time). Four out of 7 $GADA^+$ patients became persistently negative, and another 3 cases became only transiently negative after AHST; 6 islet cell antibodies $(ICA)^+$ patients became either transiently or continuously ICA^-. Only 2 cases developed insulin autoantibodies (IAA) during follow-up. These findings were consistent with the reconstitution of a tendentially anti-inflammatory environment after AHST [50].

Another Chinese study aimed to clarify the impact of a history of DKA on the outcome of AHST: Gu et al. enrolled 28 patients with a recent T1DM diagnosis (up to 26 weeks before), 11 of which presented with DKA at diagnosis. After AHST, only 3 patients with previous DKA achieved at least transient IID, versus 12 patients without previous DKA ($p = 0.051$). Moreover, the DKA patients showed a delayed response to AHST and trended towards a higher insulin dose requirement after 1 year, while in the other patients, the ongoing destruction of the remaining β-cells slowed or stopped, and the fasting C-peptide concentration and AUC increased significantly [51].

Zhang et al. found no significant difference in immune cell populations between 6 patients who became insulin-free after AHST and 3 patients who remained dependent, either pre-AHST or after 6 months; they also performed an array-based genomic study and analysed the transcriptome in the peripheral blood mononuclear cells of these patients (PBMC) [52]. They discovered that most of the immune-related genes were upregulated in both groups, except for regulatory genes such as FoxP3 and IL-10, leading to the speculation that the beneficial effects of AHST could be due to the deletion of autoreactive clones rather than the activation of immunoregulatory response. Furthermore, they identified two major gene expression pathways: the selective expression of chemokine receptors during T-cell polarization, and IL-12 and Stat4-dependent signalling pathways in Th1 development. This finding suggests a predominant differentiation of T lymphocytes in Th1 type after AHST and possibly with a new T-cell receptor (TCR) repertoire, as is consistent with observations in former systemic sclerosis studies [31][52][53].

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