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Commentary

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Prevention and treatment of type 1 diabetes: in search of the ideal combination therapy targeting multiple immunometabolic pathways

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Abstract

Type 1 diabetes (T1D) represents an autoimmune disease caused by the gradual immune-mediated destruction of the insulin-producing beta cells within the pancreatic islets of Langerhans, resulting in the lifelong need for exogenous insulin therapy. According to recent estimates, T1D currently affects about 8.4 million individuals worldwide. Since a definitive biological cure for this disease is not available yet, there is a great need for novel therapeutic strategies aimed at safely and effectively altering the natural history of the disease during its sequential stages. Ideal therapeutic goals in T1D include the prevention of autoimmune beta-cell destruction, the preservation

of residual beta-cell mass and endogenous insulin secretion, the replacement and/or regeneration of beta cells, as well as automated insulin delivery through advanced closed-loop artificial pancreas systems. With this regard, an important research area focused on the identification of a definitive biological cure for T1D is represented by the investigation of immunotherapeutic and beta-cell-protective agents used as disease-modifying therapies to forestall or eliminate insulin dependence. In this commentary, we discuss the reasons why the use of combination therapies targeting the multiple immunometabolic dysfunctions associated with T1D (other than beta-cell autoimmunity) is likely to be more effective in preserving beta cell function in individuals at different stages of T1D, as compared to the use of single therapeutic agents.

Keywords: T1D, autoimmunity, insulin secretion, C-peptide, beta-cell function, beta-cell mass, immunotherapy, beta-cell-protective agents, combination therapy

BACKGROUND

Type 1 diabetes (a.k.a. type 1 diabetes mellitus or T1DM or T1D) represents an autoimmune disease caused by the gradual immune-mediated destruction of the insulin-producing beta cells within the pancreatic islets of Langerhans, resulting in the lifelong need for exogenous insulin therapy[1]. T1D is regarded as a complex multifactorial disease, in which genetic susceptibility and environmental factors interact and promote the triggering of autoimmune responses directed against the pancreatic beta cells[2].

Human T1D represents a continuum that can be categorized into the following four sequential stages:

- **Stage 1:** individuals show islet autoimmunity (as documented by the persistent presence of at least two pancreatic islet autoantibodies) but maintain normal blood glucose values and remain asymptomatic.

- **Stage 2:** individuals maintain multiple islet autoantibody positivity and remain asymptomatic, but show abnormal blood glucose levels (dysglycemia), as documented by a glycated hemoglobin (HbA1c) value ≥ 5.7% (≥ 39 mmol/mol), impaired fasting glucose, and/or an abnormal oral glucose tolerance test.

- **Stage 3:** individuals become clinically symptomatic (clinical onset of T1D), with clinical manifestations of overt hyperglycemia and insulin deficiency such as weight loss, polyuria, polydipsia and/or fatigue, which can precede the development of diabetic ketoacidosis.

- **Stage 4:** this stage represents the postdiagnosis period of long-standing disease[3].

According to recent estimates, T1D afflicts approximately 8.4 million individuals worldwide[4]. To date, a definitive biological cure for this disease is not available yet, although there has been tremendous progress in the research field of beta-cell replacement therapies based on stem cell-derived insulin-secreting beta cells and islet encapsulation strategies, which would make it possible to perform effective pancreatic islet transplantation without the need for chronic immunosuppression in the near future[5,6]. Therefore, there is a great need for novel therapeutic strategies to safely and effectively alter the natural history of T1D during its sequential stages. Ideal therapeutic goals in T1D include the prevention of autoimmune beta-cell destruction, the preservation of residual beta-cell mass and endogenous insulin secretion, the replacement and/or regeneration of beta cells, as well as automated insulin delivery through advanced closed-loop artificial pancreas systems[7-9]. Additionally, retention of residual endogenous insulin secretion in T1D has been associated with reduced daily insulin requirements, improved glucose control, decreased risk of diabetic ketoacidosis, lower hypoglycemic episodes, lower glycemic variability, and lower chronic

microvascular complications of diabetes mellitus[10-15].

IMMUNOTHERAPEUTIC AND BETA-CELL-PROTECTIVE AGENTS AS DISEASE-MODIFYING THERAPIES FOR THE TREATMENT OF T1D

An important research area focused on the identification of a definitive biological cure for T1D is represented by the investigation of immunotherapeutic and beta-cell-protective agents able to alter the natural history (clinical onset and progression) of T1D[16]. The use of these agents can be investigated in each of the aforementioned T1D stages, including stage 4, which still represents a good time for intervention since many T1D patients retain detectable serum levels of C-peptide (a surrogate marker of endogenous insulin secretion) for several years after the disease diagnosis[3,10,17]. In this regard, it is worth reminding that the humanized anti-CD3 monoclonal antibody teplizumab (administered intravenously once a day for 14 consecutive days) was approved in November 2022 by the US Food and Drug Administration (FDA) as the first T1D disease-modifying agent able to delay the onset of stage 3 T1D in patients with stage 2 T1D aged 8 years and older[18], based on the results of a landmark phase 2, randomized, placebo-controlled, double-blind trial[19,20]. These results undoubtedly marked a turning point in the research focused on the identification of a T1D cure, making the delay of T1D progression a tangible clinical reality. Yet, in the current era of advanced diabetes technology, T1D patients should be made aware of the remarkable clinical significance of residual insulin secretion, independently of glucose control, HbA1c values and continuous glucose monitoring metrics.

Thus far, various immunotherapies have mainly been investigated in patients with new-onset T1D, even though they have most often shown no effect or only temporary beneficial effects in terms of prevention of the gradual decline in beta-cell function[7]. The cause of the poor efficacy shown by several immunotherapies in T1D is likely attributable to the multifaceted pathophysiology of this disease, which is more complex than previously thought and involves many abnormalities other than the autoimmune destruction of pancreatic beta cells and the immune-mediated decline in insulin secretion[21]. These abnormalities include the intrinsic vulnerability of beta cells to dysfunction and death[22], altered proinsulin processing[23,24], dysregulated alpha-cell glucagon secretion[25,26], early sympathetic islet neuropathy[27], histologic abnormalities of the exocrine pancreas (e.g., interacinar and intralobular fibrosis, acinar atrophy, leukocytic infiltration, fatty infiltration, pancreatic arteriosclerosis)[28], exocrine pancreatic insufficiency[29], and amylin deficiency[30], among others.

In view of the above, it seems reasonable to assume that strategies targeting only the beta-cell autoimmunity for prevention and treatment of autoimmune diabetes are likely to fail over time. Intervention studies focusing on a single therapeutic agent targeting a specific molecular signaling pathway in new-onset T1D may only result in short-term preservation of serum C-peptide levels, as has been demonstrated previously[31]. Thus, such therapeutic agents may be insufficient to significantly alter the underlying disease pathophysiology in the long term.

Based on these pathophysiological remarks, exploring the concomitant use of different immunotherapeutic and beta-cell-protective agents targeting the multiple T1D-related immunometabolic dysfunctions of the endocrine pancreas and exocrine pancreas (beyond beta-cell loss and immune-mediated insulin deficiency) is warranted in future studies, as this combination therapy approach is more likely to be effective in achieving the ultimate goals of preservation/restoration of beta-cell function and attaining insulin independence in T1D. In this context, it is worth highlighting that the immunopathological and clinical heterogeneity of T1D (with the recent discovery of new endotypes, immunotypes and theratypes of the disease)[23,32] is an additional determinant of the interindividual variability observed in the response to

distinct immunotherapies[33,34].

Moreover, it is important to outline that the efficacy of combination therapies in preserving residual beta-cell function in subjects with new-onset T1D may be further sustained by intensive insulin therapy. Indeed, it has been hypothesized that near-normalization of blood glucose levels achieved and maintained shortly after the diagnosis of T1D may help preserve endogenous insulin secretion by counteracting glucotoxicity, which has been shown to adversely affect beta-cell function in rodent models[35,36]. Among the Diabetes Control and Complications Trial (DCCT) participants diagnosed with T1D for 1 to 5 years at baseline, intensive insulin therapy was associated with higher stimulated serum C-peptide values during the first 4-5 years of the study, leading to better glucose control and reduced risk of retinopathy progression and development of microalbuminuria[11]. However, it is also worth noting that recent randomized clinical trials showed that intensive glucose control (including automated insulin delivery), as compared to standard insulin therapy, led to better glucose control but did not prevent the decline in residual C-peptide secretion after 13-24 months in youths with newly diagnosed T1D[37,38]. Thus, further studies are needed to better establish the impact of prompt intensive insulin therapy on the preservation of residual C-peptide secretion in patients with new-onset T1D.

Low-dose ATG plus pegylated G-CSF combination therapy

A randomized, single-blinded, placebo-controlled trial conducted in 25 patients with established T1D (disease duration: 4 months to 2 years; mean age ± SD: 24.6 ± 10 years) showed that combination therapy with low-dose antithymocyte globulin (ATG; a purified, pasteurized, immunoglobulin G obtained via immunization of rabbits with human thymocytes, administered intravenously at a dose of 2.5 mg/kg as 0.5 mg/kg on day 1 and as 2 mg/kg on day 2) plus pegylated granulocyte colony-stimulating factor (G-CSF, at a dose of 6 mg administered subcutaneously every 2 weeks, for a total of 6 doses) preserves beta-cell function 12 months after the therapy initiation[39]. However, among patients receiving ATG/G-CSF combination therapy, the most common worst-grade adverse events included lymphopenia (n = 15), decreased CD4 count (n = 15), hypoglycemia (n = 13), serum sickness (n = 13), and cytokine release syndrome (n = 11)[39]. Recently, promising results (in terms of prevention of T1D progression and preservation of endogenous insulin secretion) have also been observed from the off-label use of low-dose ATG in children aged 5-14 years with stage 2 T1D followed for 18-48 months[40].

VIDPP-4i combination therapy

Our group recently published a preliminary case-control study conducted in 46 children and youths with new-onset T1D, showing that the concomitant use of dipeptidyl peptidase 4 (DPP-4) inhibitor sitagliptin and vitamin D3 (VIDPP-4i combination therapy; administered orally) led to a higher frequency and duration of the clinical remission phase of T1D (also referred to as "honeymoon phase"), with 14.8% of participants remaining insulin-independent at 24 months[41]. Patients who were older than 7 years received sitagliptin 100 mg/day and vitamin D3 5,000 IU/day, while patients who were younger than 7 years were initially treated with sitagliptin at a dose of 50 mg/day and with vitamin D3 at a dose of 2,000 IU/day. Then, vitamin D3 doses were gradually adjusted in order to reach and maintain serum 25-hydroxyvitamin D values between 40 and 60 ng/mL[41]. Similarly, a multicenter, randomized-controlled trial conducted by Yan *et al.* showed positive results in patients with adult-onset T1D treated with saxagliptin (5 mg administered orally once daily) plus vitamin D3 (2,000 IU administered orally once daily), a combination therapy that led to significant preservation of beta-cell function, particularly in subjects with high glutamic acid decarboxylase antibody (GADA) levels[42]. VIDPP-4i combination therapy was safe and well tolerated in both the abovementioned studies, which did not report adverse events related to vitamin D3 and DPP-4 inhibitors[41,42].

Evidence shows that DPP-4 inhibitors and vitamin D exert synergistic immunomodulatory and anti-inflammatory actions that are protective against beta-cell autoimmunity[43]. In addition, DPP-4 inhibitors - which are medications approved for the treatment of type 2 diabetes mellitus - act by increasing the endogenous levels of the incretins GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide) and by prolonging the duration of the incretins action (through blockade of incretin degradation), thus stimulating insulin secretion, suppressing glucagon secretion, decreasing hepatic glucose production, and lowering fasting and postprandial blood glucose levels[44-46].

GABA, DPP-4i and PPI combination therapy

Another combination therapy showing promising results in preserving endogenous insulin secretion, reducing daily insulin requirements, increasing the frequency of clinical remission phase, and improving glucose control in adult T1D patients involves the concomitant use (through oral administration) of γ-aminobutyric acid (GABA; dose: 1,000-2,000 mg/day), a DPP-4 inhibitor (sitagliptin 50-100 mg/day, or saxagliptin 5 mg/day), and the proton pump inhibitor (PPI) omeprazole (dose: 20-40 mg/day)[47]. The retrospective chart review study investigating the use of this combination therapy (as an adjunct to insulin therapy) was conducted on 19 T1D patients (10 patients started the combination therapy within 12 months after the initiation of insulin therapy, while 9 patients started the combination therapy 12 months following the initiation of insulin therapy). This study did not document any adverse event related to the combination therapy with DPP-4 inhibitors, omeprazole, and GABA[47].

It is worth reminding that GABA is co-secreted with insulin by pancreatic beta cells and is known to inhibit alpha-cell glucagon secretion and promote beta-cell proliferation and survival[48]. GABA has also been shown to increase insulin sensitivity[49]. On the other hand, PPIs increase the endogenous levels of gastrin, which has been reported to promote beta-cell regeneration and ameliorate glucose tolerance in 95% pancreatectomized rats[50]. With regard to GLP-1, this gastrointestinal hormone has also been shown to stimulate beta-cell proliferation, survival, and neogenesis[48,51], besides exerting its well-established insulinotropic and glucagonostatic effects[52]. Both GLP-1 and gastrin have been shown to increase beta-cell mass and restore normoglycemia in non-obese diabetic (NOD) mice[53] and to induce beta-cell neogenesis from adult human pancreatic exocrine duct cells[54].

Autoantigen treatment with glutamic acid decarboxylase bound to aluminum hydroxide (GAD-alum)

The aim of autoantigen treatment is to reduce or halt a destructive autoimmune response by administering one or more autoantigens that may influence the dysregulated immune responses observed in autoimmune diseases such as T1D[55]. Administration of autoantigens (through a variety of routes) at different disease stages can provide sustained protection against autoimmune diseases[56]. The mechanisms of action of antigen-specific immunotherapy for T1D include the immune regulation induced against beta-cell antigen [classically associated with adaptive regulatory T-cells, transforming growth factor beta (TGF-β) and interleukin (IL)-10 induction], the immune deviation characterized by the change of dominant cellular phenotype (i.e., from Th1 to Th2), and the immune deletion of beta-cell antigen-specific T-cells[56].

Over the last decade, various studies showed that autoantigen treatment based on subcutaneous or intralymphatic administration of glutamic acid decarboxylase (GAD) bound to aluminum hydroxide (GAD-alum) can preserve endogenous insulin secretion in patients with newly diagnosed T1D, particularly in the context of a combination therapy approach[55]. GAD-alum incorporates recombinant human GAD65, which is the specific 65-kilodalton isoform of GAD expressed in human pancreatic beta cells and represents a major antigen targeted by the autoreactive T cells in T1D[57].

Studies investigating the use of subcutaneous GAD-alum in combination with oral ibuprofen and vitamin D3[58] or in combination with oral vitamin D3 and subcutaneous etanercept[59] showed that such therapeutic interventions were safe and well tolerated but did not preserve C-peptide in children and adolescents with recent-onset T1D. However, subcutaneous GAD-alum therapy has demonstrated a significant effect on the retention of C-peptide secretion, particularly in GAD autoantibody-positive patients with recent-onset T1D who carry the HLA (Human Leukocyte Antigen) DR3-DQ2 haplotype[60]. Importantly, the route of administration of GAD-alum therapy appears to play a relevant role in determining the efficacy of this autoantigen treatment. Indeed, Ludvigsson *et al.* conducted a randomized, placebo-controlled, double-blind, multicenter trial in 109 patients (aged 12-24 years) with recent-onset T1D, who had elevated serum GAD65 autoantibodies and a fasting serum C-peptide value greater than 0.12 nmol/L[61]. Participants were randomized to receive either three intralymphatic injections (performed into inguinal lymph nodes, one month apart) with 4 μg GAD-alum (on days 30, 60 and 90) and oral vitamin D (2,000 IU/day, for 120 days) or placebo. Patients treated with GAD-alum carrying the HLA DR3-DQ2 haplotype showed greater preservation of serum C-peptide Area Under the Curve ($AUC_{0\text{-}120\ min}$) during a mixed meal tolerance test after 15 months, as compared to patients with the same genotype who received placebo. With regard to adverse events, there were only mild and transient injection site reactions, with a similar frequency observed in the two study groups[61].

Interestingly, it has been documented that intralymphatic GAD-alum administration exerts immunomodulatory actions by reducing the naïve and unswitched memory B cells, increasing the follicular helper T cells, and determining the expansion of PD-1+ CD69+ cells in both CD8+ and double negative T cells[62]. Moreover, intralymphatic GAD-alum administration in T1D patients carrying the HLA DR3-DQ2 haplotype has been shown to induce a distinctive early cellular immune response as well as a predominant GAD65-induced IL-13 secretion that appears to be accompanied by a better clinical outcome[63].

The aforementioned results suggest that intralymphatic GAD-alum administration represents a well tolerated treatment that, in combination with oral vitamin D supplementation, appears to preserve C-peptide secretion in patients with new-onset T1D carrying the HLA DR3-DQ2 haplotype.

Semaglutide

Recently, a small case series enrolled 10 patients (age range: 21-39 years) who had started treatment with the GLP-1 receptor agonist semaglutide (administered subcutaneously at a dose titrated up to a maximum of 0.5 mg/week) within 3 months after the diagnosis of T1D[64]. At the time of diagnosis, the mean (± standard deviation) HbA1c value was 11.7% ± 2.1%, while the fasting C-peptide value was 0.65 ± 0.33 ng/mL. All the patients were treated with standard prandial and basal insulin. Remarkably, this study documented that semaglutide treatment (started soon after the diagnosis of T1D) led to the interruption of prandial insulin use in all patients (within 3 months) and the interruption of basal insulin use (within 6 months) in the majority of patients (7 out of 10 patients). Moreover, semaglutide treatment was associated with increased fasting C-peptide levels and better glucose control during the 12 months of observation[64]. Indeed, the fasting C-peptide value increased in all the patients to a mean of 1.05 ± 0.40 ng/mL, while the mean HbA1c value fell to 5.7% ± 0.4% at 12 months. After semaglutide dose stabilization, no hypoglycemic episodes, diabetic ketoacidosis, or other serious adverse events were reported[64].

Verapamil

Another promising drug in the setting of T1D is the antihypertensive calcium channel blocker verapamil. In a randomized, double-blind, placebo-controlled phase 2 trial conducted in 26 adults with recent-onset T1D, 12-month oral verapamil therapy (in addition to a standard insulin regimen) was well tolerated and led to an improved mixed-meal-stimulated C-peptide AUC at 3 and 12 months, fewer hypoglycemic episodes, a

lower increase in insulin requirements, and on-target glycemic control, as compared to placebo[65]. The only adverse event that was observed in a higher incidence in the verapamil group was constipation, although the reported symptoms were mild and did not need any medical intervention[65]. A subsequent double-blind, randomized clinical trial involving 88 children and adolescents with new-onset T1D demonstrated that verapamil partly preserved stimulated C-peptide secretion at 52 weeks from disease diagnosis, as compared to placebo[66]. Verapamil therapy was well tolerated. Eight participants (20%) in the placebo group and eight participants (17%) in the verapamil group had a non-serious adverse event deemed to be related to the treatment[66]. Mechanistically, it has recently been shown that verapamil normalizes the serum values of the T1D-autoantigen chromogranin A, reverses T1D-related increase in circulating pro-inflammatory T-follicular-helper cell markers, regulates the thioredoxin system, and favors an immunomodulatory, anti-apoptotic and anti-oxidative gene expression profile in human pancreatic islets[67]. Based on these findings, verapamil represents an ideal drug candidate suitable for investigation in combination therapies designed to preserve the residual beta-cell function in T1D patients during different stages of the disease.

Disease-modifying antirheumatic drugs (DMARDs): golimumab and baricitinib

Drugs that are approved for the treatment of rheumatic diseases and other autoimmune disorders, such as golimumab and baricitinib, have also been shown to exert beneficial effects in patients with new-onset T1D.

Golimumab is a human IgG1-κ monoclonal antibody specific for the human tumor necrosis factor-alpha (TNF-α) and is used for the treatment of moderate to severe rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, ankylosing spondylitis, and polyarticular juvenile idiopathic arthritis[68]. A 52-week, multicenter, placebo-controlled, double-blind, parallel-group, phase 2 trial conducted in 84 children and young adults with newly diagnosed overt (stage 3) T1D documented that golimumab (administered subcutaneously at different induction and maintenance doses based on participants' body weight) led to greater endogenous insulin secretion and less exogenous insulin use as compared to placebo[69]. Clinical benefits of golimumab treatment were substantially maintained during the subsequent 2-year follow-up period[70]. Adverse events - including infections - were similar between the golimumab group and the placebo group. No severe or opportunistic infections, neoplasms, or deaths were observed in both groups[70].

Baricitinib is a Janus kinase (JAK) inhibitor that is approved for the treatment of adults with moderately to severely active rheumatoid arthritis who have not responded adequately to conventional DMARDs, including TNF antagonist therapies[71]. Recently, in a double-blind, randomized, placebo-controlled, phase 2 trial involving 91 patients with new-onset T1D (age range: 10-30 years), baricitinib (administered orally, at a dose of 4 mg/day for 48 weeks) preserved beta-cell function (as assessed by the mixed-meal-stimulated mean C-peptide level)[72]. The frequency and severity of adverse events were similar in the baricitinib group and in the placebo group, and no serious adverse events were attributed to baricitinib or placebo[72].

DFMO (α-difluoromethylornithine or eflornithine)

Interestingly, recent evidence supports the potential effectiveness of the ornithine decarboxylase inhibitor α-difluoromethylornithine (DFMO) as a disease-modifying agent for the treatment of T1D. Intravenous DFMO (also known as eflornithine) is approved for the treatment of human African trypanosomiasis[73]. Moreover, oral DFMO has an orphan drug status for various cancers such as neuroblastoma and colon cancer[74]. In a recently published randomized controlled trial involving 41 subjects (31 of whom were children) with recent-onset T1D, DFMO was administered orally at a dose of 125-1,000 mg/m^2/day during a 3-month period (with a 3-month follow-up). The trial found that DFMO met the primary outcome of safety and tolerability, with no reports of serious adverse events or *a priori* defined dose-limiting toxicities. Furthermore, higher DFMO doses preserved C-peptide AUC by the 6-month time point after randomization, although without apparent immunomodulation[75]. Accordingly, DFMO has also been

shown to delay the onset of diabetes mellitus in preclinical models of T1D, essentially by reducing the beta-cell oxidative stress[75,76].

Antivirals: pleconaril and ribavirin

A recent phase 2 randomized controlled trial conducted on 96 children and adolescents with new-onset T1D documented that 6-month antiviral treatment with pleconaril and ribavirin (administered as oral solutions) led to significantly greater stimulated serum C-peptide AUC at 12 months, as compared to placebo[77]. The pleconaril and ribavirin combination therapy was chosen to broaden and increase the antiviral effect and to mitigate the risk of emergence of drug-resistant virus variants. Pleconaril was administered at a dose of 5 mg kg^{-1} twice daily (maximum daily dose: 600 mg), whereas ribavirin was administered at a dose of 7.5 mg kg^{-1} twice daily (maximum daily dose: 1,000 mg if body weight was less than 75 kg; 1,200 mg if body weight was more than 75 kg). The antiviral treatment was safe and well tolerated. Indeed, there were no serious adverse events in the pleconaril/ribavirin group and in the placebo group[77]. Hence, this study provided the rationale for further investigation of antiviral strategies for prevention and treatment of T1D. In keeping with these findings, viruses have long been suggested to contribute to T1D pathophysiology by triggering beta-cell autoimmunity and/or damaging pancreatic beta cells[78]. Indeed, a low-grade enterovirus infection has been documented within the pancreatic islets of subjects with newly diagnosed T1D[79].

CONCLUDING REMARKS

In light of the existing evidence, there is a need for further studies aimed at identifying the best combination therapy able to safely determine a substantial long-term preservation of endogenous insulin secretion in patients with T1D during different stages of the disease. This combination therapy may involve the use of two, three or even more anti-inflammatory, immunomodulatory, and insulinotropic/beta-cell-protective agents. We believe that future studies should also address whether combination therapies (such as VIDPP-4i) are effective in determining long-term maintenance or enhancement of preservation of beta-cell function obtained after teplizumab therapy in subjects with stage 2 T1D[20] or with new-onset T1D (stage 3 T1D)[80]. In addition, these combination therapies are worth being investigated even in other T1D settings, such as in patients undergoing pancreatic islet transplantation and novel stem cell-derived islet cell therapies (e.g., encapsulated stem cell-based therapy for beta-cell replacement), in order to establish whether they can contribute to forestalling insulin dependence and sustaining the long-term insulin independence after successful transplantation. In view of the recent encouraging results coming from studies conducted in T1D patients and investigating the use of drugs that are approved and commonly used for treatment of other diseases such as type 2 diabetes mellitus, rheumatic diseases, other autoimmune disorders, bone diseases, and viral and parasitic infections (i.e., DPP-4 inhibitors, GLP-1 receptor agonists, golimumab, baricitinib, vitamin D, pleconaril, ribavirin, DFMO), drug repurposing for treatment of T1D may yield surprising results in future (large) studies. In conclusion, future intervention trials enrolling subjects with T1D at different stages of the disease should primarily aim to investigate the concomitant use of different drugs acting on multiple T1D-related immunometabolic abnormalities, in pursuit of the best combination therapy for safe and prolonged preservation of endogenous insulin secretion in different endotypes and immunotypes of T1D.

DECLARATIONS

Authors' contributions

Conceptualization, Writing-original draft preparation: Pinheiro MM, Infante M
Writing-review and editing: Pinheiro FMM, Garo ML, Pastore D, Pacifici F, Ricordi C, Della-Morte D

Reading and agreeing the published version of the manuscript: Pinheiro MM, Pinheiro FMM, Garo ML, Pastore D, Pacifici F, Ricordi C, Della-Morte D, Infante M

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