

# GLP-1 receptor agonists can reverse immunosuppression-induced beta-cell dysfunction

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## ABSTRACT

**It is well known that some of the agents commonly used during immunosuppressive (IS) therapy after solid organ transplantation can contribute to beta cell dysfunction and result in diabetes mellitus in the transplant recipient. Some of the risks associated with post-transplant diabetes mellitus (PTDM) include cardiovascular disease (CVD), graft failure and mortality. Since this significance was recognized, many studies are ongoing to refine the IS therapy regimen to reduce or discontinue corticosteroids and calcineurin inhibitors (CNI).**

**A promising addition to the immunosuppression treatment regimen to treat PTDM is glucagon-like peptide-1 receptor (GLP-1R) agonists or incretin mimetics normally used in the treatment of type 2 diabetes (T2D). Studies show that adding GLP-1R agonists to the immunosuppression regimen after solid organ transplant is beneficial not only for the health of the islet beta cells but also positively affects immune function in metabolic disorders by suppressing the activation of CD4+ T lymphocyte cytokine expression. Additional benefits include decreased cardiac graft vasculopathy, improvement of hepatic steatosis, preservation of kidney function, enhanced graft survival and improved all-cause mortality rates for solid organ transplant recipients.**

## ABBREVIATIONS

AATG = rabbit antithymocyte globulins, Aza = azathioprine, CD26 = cluster of differentiation antigen 26, CNI = calcineurin inhibitors, Cn/NFAT = calcineurin/Nuclear Factor of Activated T cells, CsA = cyclosporine A, DCG = dense core gran-

ule, CV = cardiovascular, CVD = cardiovascular disease, DPP-4 = dipeptidyl peptidase-4, DPP-4i = dipeptidyl peptidase-4 inhibitors, GCs = glucocorticoids, GLP-1R = Glucagon-like peptide-1 receptor, HbA1c = glycated hemoglobin, IS = Immunosuppression, MMF = mycophenolate mofetil, mTOR = mammalian target of rapamycin, PPAR- $\gamma$  = peroxisome proliferator-activated receptor gamma, PTDM = post-transplant diabetes mellitus, SGLT2 = sodium-glucose cotransporter 2, SOT = solid organ transplant, T2D = type 2 diabetes, Tac = tacrolimus, TGF- $\beta$ 1 = transforming growth factor- $\beta$ 1, TZD = thiazolidinediones.

## INTRODUCTION

With all the success achieved in solid organ transplants (SOT) there is nevertheless room for improvement. Immunosuppression (IS) is required to keep the immune system of the recipient from rejecting the allogeneic tissue of the donor. However, because of the complexity of the human immune system and our efforts to quell it, the adverse effects of long-term IS are still being discovered and addressed. Historically, immunosuppression was limited to inhibiting T-cells in the recipient first with whole body irradiation then with steroids, neither of which succeeded at improving graft survival. Then with the development of tissue matching of the donor to the recipient in the early 1960s, and a combination of drugs like azathioprine and steroids, graft survival improved, and SOTs became more widespread. When cyclosporine came into use in the 1980s, 1-year graft survival rates improved from 50% to 80%<sup>1</sup>. Novel agents, including antibodies and fusion proteins against specific targets of the immune system have been introduced over time and today, most IS cocktails contain several of the following: rab-

bit antithymocyte globulins (ATG), basiliximab, alemtuzumab, corticosteroids, tacrolimus (Tac), cyclosporine A (CsA), azathioprine (Aza), mycophenolate mofetil (MMF), sirolimus (rapamycin), everolimus, belatacept, intravenous immunoglobulin and rituximab (Table 1)<sup>1-3</sup>. However, despite the success of these drugs in preventing organ rejection, some of them have been linked to ad-

verse events that include post-transplant diabetes mellitus (PTDM).

#### IMMUNOSUPPRESSION AND POST-TRANSPLANT DIABETES MELLITUS

IS needs to be administered for the life time of the organ recipient. However, long-term treatment with some of the most common agents included in IS

**Table 1.** Immunosuppressive agents and their association with PTDM.

IS Agent	Activity of drug	PTDM Risk	Glycemic Effect	Notes	References
Antithymocyte globulins (ATG)	T-cell inhibitor	Low	• No impact	Induction IS	Jasiak et al <sup>1</sup> Black et al <sup>2</sup> Shivaswamy et al <sup>3</sup> Munshi et al <sup>7</sup>
Basiliximab	IL-2 receptor antagonist	Increased	• Impaired glucose homeostasis	Induction IS	Jasiak et al <sup>1</sup> Shivaswamy et al <sup>3</sup> Munshi et al <sup>7</sup>
Alemtuzumab (Campath-1H)	Humanized anti-CD52 monoclonal antibody for lymphocyte depletion	Low	• No impact	Induction IS	Jasiak et al <sup>1</sup> Black et al <sup>2</sup>
Corticosteroids	Steroid	High	• Increased hepatic gluconeogenesis • Peripheral insulin resistance • Dyslipidemia	Induction IS, Maintenance IS	Jasiak et al <sup>1</sup> Black et al <sup>2</sup> Munshi et al <sup>7</sup> Ducloux et al <sup>12</sup> Chowdhury et al <sup>13</sup> Shapiro et al <sup>14</sup> McMahon et al <sup>15</sup> Penfornis et al <sup>16</sup> Ahmed et al <sup>29</sup>
Tacrolimus/ FK506 (Tac)	Calcineurin inhibitor	High	• Beta cell apoptosis • Peripheral insulin resistance • Decreased insulin secretion	Maintenance IS	Jasiak et al <sup>1</sup> Black et al <sup>2</sup> Chowdhury et al <sup>13</sup> Ducloux et al <sup>12</sup> Chowdhury et al <sup>13</sup> Shapiro et al <sup>14</sup> Penfornis et al <sup>16</sup> Ahmed et al <sup>29</sup> Cehic et al <sup>57</sup>
Cyclosporine A (CsA)	Calcineurin inhibitor	High	• Hyperglycemia • Insulin resistance • Decreased insulin secretion	Maintenance IS	Jasiak et al <sup>1</sup> Black et al <sup>2</sup> Cehic et al <sup>57</sup>
Azathioprine (Aza)	Prevents T-cell proliferation by inhibiting purine synthesis	Low	• No impact	Maintenance IS	Jasiak et al <sup>1</sup> Shivaswamy et al <sup>3</sup> Cehic et al <sup>57</sup>
Mycophenolate mofetil (MMF)	Prevents T-cell proliferation by depleting guanosine nucleotides	Low	• No impact	Maintenance IS	Jasiak et al <sup>1</sup> Shivaswamy et al <sup>3</sup> Munshi et al <sup>7</sup> Cehic et al <sup>57</sup> Barlow et al <sup>73</sup>

*Continued*

**Table 1 (continued).** Immunosuppressive agents and their association with PTDM.

IS Agent	Activity of drug	PTDM Risk	Glycemic Effect	Notes	References
Sirolimus (rapamycin)	mTOR inhibitor	Increased	<ul style="list-style-type: none"> <li>Increased beta cell apoptosis</li> <li>Reduced beta cell proliferation</li> <li>Dyslipidemia</li> <li>Peripheral insulin resistance</li> <li>Dose-dependent hyperglycemia</li> </ul>	Maintenance IS	Jasiak et al <sup>1</sup> Shivaswamy et al <sup>3</sup> Cehic et al <sup>57</sup> Barlow et al <sup>73</sup>
Everolimus	mTOR inhibitor	Increased	<ul style="list-style-type: none"> <li>Insulin resistance</li> <li>Decreased insulin secretion</li> </ul>	Maintenance IS	Jasiak et al <sup>1</sup> Shivaswamy et al <sup>3</sup> Cehic et al <sup>57</sup>
Belatacept	Targets CD80/86 blocking T-cell costimulation pathway	Low	<ul style="list-style-type: none"> <li>Lowered HbA1c</li> </ul>	Maintenance IS but rejection events occurred when used without CNIs or steroids	Jasiak et al <sup>1</sup> Jenssen et al <sup>5</sup> Terrec et al <sup>20</sup>
Rituximab	Targets CD20 antigen on B cells	Low	<ul style="list-style-type: none"> <li>Slight chance of hyperglycemia due to a decrease in insulin secretion</li> </ul>	Off-label use for kidney transplants but showed increased rate of infections including CMV	Jasiak et al <sup>1</sup>
Intravenous immunoglobulin (IVIG)	Role in immunomodulation is complex and not clearly understood	None	<ul style="list-style-type: none"> <li>No impact</li> </ul>	Reduces T-cell activation, induces B cell apoptosis and inhibits complement	Jasiak et al <sup>1</sup>
Daclizumab	Humanized mab, binds to CD25, the alpha subunit of the IL-2 receptor on T cells	Low	<ul style="list-style-type: none"> <li>May cause hyperglycemia</li> <li>May cause liver complications</li> </ul>	Induction IS, withdrawn from global market due to incidents of encephalitis	Jasiak et al <sup>1</sup> Black et al <sup>2</sup> Penfornis et al <sup>16</sup> Penfornis et al <sup>16</sup> Bianchi et al <sup>74</sup>

*Abbreviations:* CMV = cytomegalovirus, HbA1c = glycated hemoglobin, IL-2 = interleukin 2, IS = immunosuppression, mab = monoclonal antibody, mTOR = mammalian target of rapamycin, PTDM = post-transplant diabetes mellitus.

cocktails are associated with unfavorable consequences including PTDM. The incidence of PTDM is difficult to determine, with reports ranging from 2%-74%<sup>3-7</sup> and PTDM cannot be underestimated as a cause for increased risk of cardiovascular morbidity and all-cause mortality in transplant patients<sup>8-10</sup>.

#### MOST SIGNIFICANT CULPRITS

As far back as 1964, Starzl et al<sup>11</sup> noted new onset diabetes in patients after kidney transplantation. Some immunosuppressive agents are more prone to cause impaired glucose tolerance and

post-transplant diabetes than others. Arguably, at the top of the list are corticosteroids and calcineurin inhibitors such as tacrolimus/FK506 (Tac) and cyclosporine A (CsA)<sup>12-14</sup>. Corticosteroids increase both hepatic glucose production through gluconeogenesis stimulation and peripheral insulin resistance<sup>15</sup>. As for calcineurin inhibitors, there is a direct correlation between the effect on insulin secretion and dose administered<sup>16</sup>. It has been documented that diabetes caused by drugs like Tac and CsA can be partially abrogated or completely reversed by lowering

the dose or switching to a different immunosuppressant<sup>17-20</sup>. Both sirolimus and everolimus function as inhibitors of the mammalian target of rapamycin (mTOR) and improvement of glucose intolerance and dyslipidemia have been reported when the dose of mTOR inhibitors are reduced<sup>3</sup>. Sirolimus, tacrolimus and everolimus have been shown to reduce beta cell mass through apoptosis and all have an anti-proliferative effect on beta cells<sup>3</sup>. Other IS agents such as MMF, belatacept and Aza have not been shown to have an impact on glucose metabolism or insulin secretion (Table 1).

#### HOW IMMUNOSUPPRESSION AFFECTS GLUCOSE METABOLISM AND INSULIN SECRETION

Normal beta cell development from birth encompasses two important functions. The first is responsiveness to glucose. This incorporates the ability to increase insulin production after sensing an increase in blood glucose levels. Mature beta cells must have the ability to generate and store insulin in secretory granules within the cell in preparation for release when needed to metabolize glucose. The second function of central importance is the ability of beta cells to expand to an appropriate mass as the organism grows to adulthood. Glucokinase is a crucial regulator of beta cell maturation and proliferation. It has been shown to ultimately stimulate pathways that lead to insulin production, secretion and proliferation<sup>21-25</sup>. The calcineurin/Nuclear Factor of Activated T cells (Cn/NFAT) pathway that manages the proliferation, survival and differentiation of many cell types including lymphocytes and neurons has also been implicated in the regulation of beta cell function<sup>26</sup>. Based on the observation that 10%-30% of transplant patients receiving calcineurin inhibitors such as tacrolimus developed diabetes mellitus, Goodyer et al<sup>27</sup> generated a genetically modified mouse to test the role of Cn/NFAT. Their results indicate that Cn/NFAT signaling is required during beta cell maturation for expression of insulin, Pdx1, Glut2 and glucokinase genes in mice and that Cn/NFAT signaling regulates expression of beta cell dense core granule (DCG) formation. Experiments exposing juvenile human islets to tacrolimus showed a similar reduction of gene expression encoding DCG components, and, therefore, Cn/NFAT signaling<sup>27</sup>.

The means by which glucocorticoids (GCs) affect glucose homeostasis are complex and not well understood; however, GCs exert the majority of their effects on glucose metabolism through activation of glucocorticoid receptors. GCs are naturally produced by the adrenal cortex in response to stress. Long-term excess of endogenous or exogenously administered GCs impacts all aspects of glucose metabolism including hepatic gluconeogenesis and impaired insulin sensitivity at the level of skeletal muscle and adipose tissue, resulting in hyperglycemia and dyslipidemia. Clinically, chronic excessive GC signaling is associated with Cushing syndrome and possibly metabolic syndrome<sup>28</sup>. In most cases, glucose regulation is restored once the corticosteroids are discontinued<sup>29</sup>. The incidence of hyperglycemia in post-transplant patients receiving corticosteroids is reportedly a substantial 17%-32%<sup>30</sup>.

#### THE ROLE OF GLUCAGON-LIKE PEPTIDE-1 IN METABOLISM

Glucagon-like peptide-1 (GLP-1) is a hormone classified as an incretin that responds to an increase in blood glucose levels by promoting insulin secretion. It is produced mainly by enteroendocrine L cells in the distal ileum and colon during the post-translational processing of the proglucagon peptide and is upregulated rapidly by food intake. In the periphery, GLP-1 affects gut motility as well as inhibits glucagon secretion and gastric acid secretion<sup>31</sup>. There is also an effect on appetite and weight control via the central nervous system<sup>32,33</sup>. One of the most significant effects of GLP-1 is regulating beta-cell function. It is believed to enhance insulin secretion through the control of ion channels involved in  $K_{ATP}$ -dependent insulin secretion<sup>31</sup>. GLP-1 stimulates beta cell  $Ca^{2+}$  transients through the GLP-1R and these are known to activate the calcium-dependent Cn/NFAT signaling pathway that regulates beta cell proliferation and function in juvenile and adult islets<sup>34,35</sup>.

The GLP-1 peptide hormone is rapidly degraded by dipeptidyl peptidase-4 (DPP-4) also known as cluster of differentiation antigen 26 (CD26) and neutral endopeptidase 24.11 (NEP 24.11) with a half-life of about 2 minutes<sup>31</sup>. GLP-1 functions by coupling to its specific G-protein receptor, the GLP-1 receptor (GLP-1R) that is expressed mainly in pancreatic beta cells. Because of the rapid de-

struction of the molecule, T2D therapies have focused on treatments such as GLP-1R agonists or DPP-4 inhibitors (DPP-4i) to increase GLP-1 activity. In T2D patients, GLP-1R agonists are associated with improved glycemic control, weight loss, cardiovascular protection and, unlike other secretagogues such as sulfonylureas, lower risk of hypoglycemia<sup>33,36,37</sup>.

### INCRETIN-BASED THERAPIES

There are 2 classes of drugs aimed at modulating the amount of the incretin hormone GLP-1 in the circulation. These are first, the GLP-1R agonists that mimic the action of GLP-1 but are more resistant to rapid inactivation by DPP-4 and second, the DPP-4i that prevent the degradation of endogenous GLP-1<sup>38</sup>. Found largely in pancreatic beta cells, GLP-1R are also amply present in the gut and central nervous system and to a lesser extent in the heart, lungs, kidney vasculature, pancreatic alpha cells and peripheral nervous system<sup>33</sup>. The mechanism of incretin-based agents is glucose-dependent and so the risk of hypoglycemia is minimal.

In 2005 the first GLP-1R agonist therapy approved for use in humans was exenatide. It is a first-in-class diabetes therapy that uses an incretin hormone for metabolic control<sup>39</sup>. Exenatide is a synthetic version of Exendin-4 that is a naturally occurring component of Gila monster venom first described by Raufman et al<sup>40</sup> in 1982 who then further explored the peptide in a subsequent study<sup>41</sup>. Liraglutide is long-acting GLP-1R agonist and has been found to inhibit cytokine production (IFN-gamma and IL-4) by activated CD4<sup>+</sup> T cells. It has been shown to be effective not only at improving glucose homeostasis in T2D and promoting weight loss but also at preventing hepatic lipid buildup (hepatic steatosis) in mice<sup>42</sup> and humans<sup>32,43</sup>. All the incretin mimetics have similar effects such as stimulation of glucose-dependent insulin release, suppression of glucagon secretion and induction of weight loss. Slower gastric emptying has been associated with short-acting GLP-1R agonists such as short-acting exenatide<sup>44</sup> and therefore may slow the absorption of IS agents<sup>45</sup>. Cardioprotective effects have been reported in clinical trials, including ELIXA, LEADER, SUSTAIN-6 and REWIND, that focused on the evaluation of GLP-1R agonists and cardiovascular (CV) disease in di-

abetic patients. It was reported that liraglutide, semaglutide and dulaglutide, but not lixisenatide, showed a significant reduction of macrovascular CV events<sup>32,37,38,46</sup>. Table 2 lists the most common GLP-1R agonists and their brand names, SOTs that have included them in maintenance therapy, and some outcomes (Table 2).

The most common adverse effect of incretin mimetics seems to be nausea that usually resolves over time, but more troubling are reports of incidents of acute pancreatitis, pancreatic cancer, and other malignant neoplasms<sup>47</sup>. These would seem to make GLP-1R agonists less than ideal. However, based on a meta-analysis of the outcomes of CV clinical trials that included incretin-based glucose-lowering medications, the actual increased risk of these incidents that can be attributed to GLP-1R agonists or DPP-4i therapy is negligible<sup>47</sup>.

DPP-4i, also known as gliptins, act to extend incretin function by preventing the degradation of GLP-1 and a similar incretin, gastric inhibitory polypeptide (GIP). DPP-4i are currently used in combination with other T2D drugs to increase insulin secretion and decrease glucagon secretion and glucotoxicity. Studies have shown that DPP-4 has non-incretin substrates and immunomodulatory activity that cleaves cytokines, chemokines and neuropeptides involved in inflammation, immunity and vascular function<sup>48</sup>. In light of this, DPP-4i may protect T2D patients against CVD and microvascular diabetic complications through both GLP-1 and non-GLP-1 dependent mechanisms<sup>49,50</sup>. Moreover, in pre-clinical and clinical studies, DPP-4i were shown to exert anti-inflammatory and immunomodulatory effects that may contribute to graft survival and inhibit graft dysfunction<sup>51,52</sup>. To date, there are a few reports of DPP-4i being used to alleviate PTDM. Jin et al<sup>53</sup> showed that a DPP-4i improved Tac-induced islet injury and hyperglycemia in rats. In a clinical retrospective cohort study targeting kidney transplant recipients with PTDM, the DPP-4i drug linagliptin was effective in controlling hyperglycemia and led to blood glucose levels comparable to those of kidney graft recipients without PTDM<sup>54</sup>. In another study, lung graft recipients that included a DPP-4i in their treatment had a higher level of the anti-inflammatory cytokine IL-10 at 6 months after transplant resulting in less allograft dysfunction compared to recipients who did not

**Table 2.** GLP-1 receptor agonists and their clinical use as adjunctive therapy in organ recipients with PTDM.

Name	Alternative/ Brand names	Transplanted Organ	Outcomes	References
<b>Liraglutide</b> Long-acting (~13 hours)	Victoza® Saxenda®	Kidney Liver Heart Pancreas Lung	<ul style="list-style-type: none"> <li>• Does not affect Tac levels</li> <li>• Reduces risk of cardiovascular events</li> <li>• May cause renal impairment</li> <li>• Best at reducing HbA1c</li> <li>• Reduces appetite</li> <li>• Inhibits cytokine production by T cells</li> <li>• Suppresses glucagon secretion and hepatic glucose production</li> <li>• Increases insulin secretion</li> <li>• Potential risk of thyroid tumor*</li> </ul>	Andersen et al <sup>32</sup> Caprio et al <sup>37</sup> Nauck et al <sup>38</sup> Ohki et al <sup>43</sup> Pantalone et al <sup>46</sup> Cehic et al <sup>57</sup> Nauck et al <sup>75</sup>
<b>Dulaglutide</b> Long-acting (4-5 days)	Trulicity®	Kidney Liver Heart	<ul style="list-style-type: none"> <li>• Suppresses glucagon secretion and hepatic glucose production</li> <li>• Reduces risk of cardiovascular events</li> <li>• Increases insulin secretion</li> <li>• Potential risk of thyroid tumor*</li> </ul>	Andersen et al <sup>32</sup> Caprio et al <sup>37</sup> Nauck et al <sup>38</sup> Pantalone et al <sup>46</sup> Cehic et al <sup>57</sup> Nauck et al <sup>75</sup>
<b>Exenatide</b> Short-acting (~2.5 hours)	Exendin-4 Byetta® Bydureon®	Islets of Langerhans	<ul style="list-style-type: none"> <li>• Nausea, vomiting and diarrhea that decrease with time</li> <li>• Possible hypoglycemia</li> <li>• Acute pancreatitis reported</li> <li>• Renal impairment</li> <li>• Reduces liver fat</li> <li>• May inhibit beta-cell apoptosis</li> <li>• Delays gastric emptying (reduces postprandial glucose excursions)</li> <li>• Increases insulin secretion</li> <li>• Potential risk of thyroid tumor*</li> </ul>	Parkes et al <sup>39</sup> Raufman et al <sup>40</sup> Raufman et al <sup>41</sup> Gentilella et al <sup>44</sup> Vanhove et al <sup>45</sup> Abd El Aziz et al <sup>47</sup> Aroor et al <sup>50</sup> Cehic et al <sup>57</sup> Nauck et al <sup>75</sup>
<b>Exenatide extended-release</b> Long-acting (administered once weekly)	Bydureon BCise®	Islets of Langerhans	<ul style="list-style-type: none"> <li>• Nausea, vomiting and diarrhea that decrease with time</li> <li>• Possible hypoglycemia</li> <li>• Acute pancreatitis reported</li> <li>• Renal impairment</li> <li>• Reduces liver fat</li> <li>• May inhibit beta-cell apoptosis</li> <li>• Reduces both fasting glucose and postprandial glucose</li> <li>• Increases insulin secretion</li> <li>• Potential risk of thyroid tumor*</li> </ul>	Parkes et al <sup>39</sup> Raufman et al <sup>40</sup> Raufman et al <sup>41</sup> Abd El Aziz et al <sup>47</sup> Aroor et al <sup>50</sup> Cehic et al <sup>57</sup> Nauck et al <sup>75</sup>

*Abbreviations:* HbA1c = glycated hemoglobin, PTDM = post-transplant diabetes mellitus.

\*Reported in animal studies, actual risk for humans is unclear.

receive DPP-4i<sup>52</sup>. For a study involving DPP-4i after pancreatic transplant, the recipients receiving sitagliptin did not require insulin for a longer period of time than recipients receiving standard therapy<sup>55</sup>. The sparse clinical studies mainly covered safety and efficacy in the short-term period. Although there seems to be beneficial outcomes for including DPP-4i in after-transplant therapy,

there is limited information available concerning the long-term use of DPP-4i in PTDM<sup>56</sup>.

#### WHICH TRANSPLANT RECIPIENTS ARE AT RISK FOR PTDM?

Incidence of PTDM for the most common organ transplants are wide-ranging. Estimates included from different sources are as follows: kidney

4%-74%, heart 4%-40%, lung 20%-40% and liver 2.5%-40%<sup>3,5,7</sup>. There are several known risk factors for development of PTDM and many of them are the same as the risks for developing T2D such as increasing risk with age (>40 y), body mass index (BMI, >25kg/m<sup>2</sup>), genetics, family history of T2D, high-risk ethnicity, infections (hepatitis C and cytomegalovirus), cystic fibrosis and polycystic kidney disease. Post-transplant risk factors include type of organ transplanted, post-transplant weight gain, and large doses of IS agents such as prednisolone, Tac and sirolimus<sup>3,5,13,29</sup>. PTDM has been reported to be decreasing in kidney transplant patients while occurrence in heart transplant patients seems to be increasing<sup>57</sup>.

Pre-operation screening such as oral glucose tolerance tests of transplant candidates for insulin resistance/glucose intolerance could be used as an effective predictor of PTDM and prophylactic therapy (including GLP-1R agonists) may be initiated before the transplant surgery in order to alleviate the transplants-related metabolic consequences<sup>58</sup>. Identification and early management of individuals that are susceptible to develop PTDM would improve quality of life for the patient, extend the functional life of the grafted organ and reduce mortality.

#### ARE GLP-1R AGONISTS EFFECTIVE IN TREATING PTDM?

As yet, there have been very few targeted clinical trials that focus on the use of GLP-1R agonists in transplant recipients<sup>59</sup>. There are, however, retrospective studies and animal experiments that establish the benefit of including a GLP-1R agonist as part of the post-transplant adjunctive therapy. Dai et al<sup>60</sup> showed that Exendin-4 was able to completely rescue Tac-induced beta cell dysfunction and partially rescue sirolimus-induced beta cell dysfunction in mice. Also in mice, Wang et al<sup>61</sup> concluded that liraglutide alleviates heart graft vasculopathy and fibrosis partially by inhibiting transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1) expression.

Several retrospective or observational clinical studies in T2D or PTDM patients show that treatment with a GLP-1R agonist improved glycemic control and promoted weight loss while having no effect on Tac levels. The PTDM patients included recipients of kidney, heart, pancreas and liver transplants<sup>62-66</sup>. Singh et al<sup>64</sup> reported improvement in chronic kidney disease after treatment with dula-

glutide, as well as a sustained reduction in weight, insulin requirement and improved HbA1c values in 63 SOT recipients, independent of type of transplant.

#### IS THERE ANY ALTERNATIVE TO GLP-1R AGONISTS?

Other, older drugs that are commonly used for control of T2D by improving insulin resistance are the thiazolidinediones (TZDs) also known as glitazones. TZDs such as rosiglitazone and pioglitazone are agonists of peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ )<sup>57</sup>. These are considered third-line medications and are usually not administered unless primary and secondary T2D medications, such as insulin, metformin and sulfonylureas, are inadequate at achieving glucose control. TZDs are not known to interact with CNIs but their safety and efficacy for treatment of PTDM has yet to be established<sup>16</sup>. This class of drugs has been linked to serious adverse events such as weight gain, edema, heart failure and bladder cancer<sup>57,67</sup> and are therefore not recommended for management of PTDM after heart transplantation (Table 3). Rosiglitazone has subsequently been withdrawn from several markets in the world due to higher CV risk including stroke<sup>68</sup>.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce glucose reabsorption in the kidney and promote urinary glucose excretion. There is merit for including these agents in treating PTDM as they were tested in T2D patients and found to significantly reduce cardiovascular events and kidney disease progression<sup>69</sup> and cannot cause hypoglycemia because they work independently of beta-cell function and insulin secretion. Clinical trials using the SGLT2 inhibitor empagliflozin for PTDM after kidney<sup>70,71</sup> and heart<sup>72</sup> transplantation have shown promising preliminary results including patient safety, good metabolic control, and reduction in weight with no significant changes in blood pressure or renal function (Table 3).

#### CONCLUSIONS

GLP-1 agonists are very attractive in treating PTDM due to their low hypoglycemia risk and their lack of interaction with common immunosuppressive agents. Clearly, more clinical trials are needed to further explore the routine addition of incretin mimetics to immunosuppression regimens of those patients at risk of developing PTDM.

**Table 3.** Alternatives to GLP-1 receptor agonists in organ recipients with PTDM.

Name	Alternative/ Brand names	Transplanted Organ	Outcomes	References
<b>Thiazolidinediones (glitazones)</b>	Rosiglitazone (Avandia®)	Kidney	<ul style="list-style-type: none"> <li>• Improved insulin sensitivity</li> <li>• Edema</li> <li>• Weight gain</li> <li>• Macular edema</li> <li>• Heart failure</li> </ul>	Penfornis et al <sup>16</sup> Cehic et al <sup>57</sup> Zhu et al <sup>67</sup> Lu et al <sup>68</sup>
	Pioglitazone (Actos®)			
<b>SGLT2-inhibitors (gliflozins)</b>	Empagliflozin (Jardiance®)	Kidney Heart	<ul style="list-style-type: none"> <li>• Increased urinary/genital infections</li> <li>• Hypoglycemia if combined with sulfonylureas or insulin</li> <li>• Greater risk of ketoacidosis in transplant patients</li> <li>• Reduced renal glucose reabsorption</li> </ul>	Chilton et al <sup>69</sup> Halden et al <sup>70</sup> Schwaiger et al <sup>71</sup> Cehic et al <sup>57</sup> Cehic et al <sup>72</sup>

*Abbreviations:* PTDM = post-transplant diabetes mellitus, SGLT2 = Sodium-glucose cotransporter 2.

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