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DRUG DISCOVERY

A View on the first dipeptidyl peptidase 4 inhibitor - Sitagliptin

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ABSTRACT

Sitagliptin is a dipeptidyl-peptidase inhibitor (DPP-4 inhibitor) that has recently been approved for the therapy of type 2 diabetes. Like other DPP-4 inhibitors its action is mediated by increasing levels of the incretin hormones glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP). Sitagliptin is effective in lowering HbA1c, and fasting as well as postprandial glucose in monotherapy and in combination with other oral antidiabetic agents. It stimulates insulin secretion when hyperglycemia is present and inhibits glucagon secretion. In clinical studies it is weight neutral. This article gives an overview of the mechanism of action, the pharmacology, and the clinical efficacy and safety of sitagliptin in type 2 diabetes therapy.

1. INTRODUCTION

Since glucagon-like peptide-1 (GLP-1) itself is not feasible for type 2 diabetes therapy due to its very short biological half-life, two major strategies have been developed to utilize the beneficial effects of GLP-1. On the one hand, long-acting, dipeptidyl-peptidase ihibitor (DPP-4 inhibitor)-resistant peptides with a high similarity to the native GLP-1 can be used as injectable therapeutic agents (incretin mimetics or GLP-1 analogues). Exendin-4, or exenatide in the recombinant form, is such a peptide originally found in the saliva of the gila monster. Exenatide has a very high amino acid sequence similarity with GLP-1 and is a GLP-1 receptor agonist. It has been approved for type 2 diabetes therapy for patients having insufficient glucose control under a therapy with metformin, sulfonylureas, or a combination of both under the trade name Byetta® (Eli Lilly Pharmaceuticals, Indianapolis, IN, USA and Amylin Pharmaceuticals, San Diego, CA, USA). Liraglutide is a GLP-1 analogue under development by Novo Nordisk Pharmaceuticals (Copenhagen, Denmark) and is being evaluated for efficacy and safety in type 2 diabetes in clinical studies in phase III.

DPP-4 inhibition in type 2 diabetesThe incretin effect is diminished in type 2 diabetes. Raising concentrations of intact GLP-1 can lower or even normalize plasma glucose in type 2 diabetic patients. GLP-1 is degraded very rapidly by DPP-4, an enzyme that is localized vastly in the endothelium and can also be measured in the circulation. DPP-4 cleaves peptides with an N-terminal alanine or proline amino acid residue. The two GLP-1 fragments resulting from DPP-4 activity are both biologically inactive, the fragment GLP-1(9-36) amide has even been described as having GLP-1 antagonistic properties in some studies. DPP-4 inhibition raises intact GLP-1 plasma concentrations to levels observed in the stimulated state after a meal. Besides GLP-1, which has a very high affinity towards DPP-4 as a substrate, other peptides, such as glucose-dependent insulinotropic peptide (GIP), pituitary adenylate cyclase-activating polypeptide (PACAP), and gastrin-releasing peptide (GRP) (see Table 1) are also inactivated by DPP-4 by enzymatic cleavage. Some of these peptides also play a role in glucose homeostasis (Nauck and El-Ouaghlidi 2005). DPP-4 is also expressed on T-lymphocytes where it has also been described as CD-26 receptor. The effect of pharmacological inhibition of this receptor with DPP-4 inhibitors has not been completely clarified yet, but so far, the DPP-4 inhibitors in development for the treatment of type 2 diabetes have not shown any immunological adverse effects in this respect. Besides DPP-4, other dipeptidyl peptidases such as DPP-8 or DPP-9 also degrade peptide hormones. In the development of DPP-4 inhibitors it was important to have a high specificity for DPP-4 and no inhibitory activity towards the other DPPs.

2. SITAGLIPTIN PHOSPHATE FOR PATIENTS WITH TYPE 2 DIABETES

By inhibiting DPP-4, sitagliptin enhances postprandial levels of active glucagon-like peptide-1 (GLP-1), leading to a rise in insulin release and decrease in glucagon secretion from pancreatic α-cells. Sitagliptin is 87% orally bioavailable, undergoes minimal hepatic metabolism, and is primarily excreted unchanged (~79%) in the urine. At doses ≥100 mg QD, DPP-4 activity is inhibited by >80%, with a consequent 2-fold rise in active GLP-1 levels. The reduction in glycosylated hemoglobin (HbA1c) observed with 100 mg QD of sitagliptin in Phase III monotherapy trials ranged from ~0.5% to 0.6% ($P \leq 0.001$ vs placebo). In Phase III combination trials, HbA1c was reduced by ~0.7% when added to metformin and ~0.9% with pioglitazone ($P < 0.001$ vs placebo). Markers of β-cell function, including proinsulin/insulin ratio and homeostasis model assessment of β-cell function, were improved with sitagliptin treatment. In studies, sitagliptin has been well tolerated, significant hypoglycemia and weight gain have not been noted. When used alone or in combination with metformin or pioglitazone, sitagliptin has been associated with significant reductions in HbA1c and has been well tolerated. Before its place in therapy can be firmly established, long-term studies evaluating the safety of prolonged DPP-4 inhibition are necessary. Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, is a newly developed oral hypoglycemic agent. Sitagliptin increases the level of glucagon-like polypeptide (GLP)-1 that increases insulin secretion. In addition, GLP-1 decreases salt intake and increases urinary salt excretion. Therefore, the sitagliptin treatment might lower blood pressure in hypertensive patients with type 2 diabetes. It also remains to be examined whether the reduction in blood pressure with sitagliptin treatment is related to the blood glucose improvement and the body weight decrease. To identify beneficial effects of sitagliptin treatment, we administered sitagliptin (50 mg) on alternate days to seventeen type 2 diabetes outpatients with insufficient blood glucose control (8 males and 9 females, mean age of 67.1 years). The patients were also treated with oral hypoglycemic agents and antihypertensive drugs for six months before and during the sitagliptin administration. We measured the level of hemoglobin (Hb) A1c, systolic blood pressure (SBP), and body mass index (BMI) for up to six months thereafter. Their BMIs remained unchanged. The levels of HbA1c were dropped from 6.5 ± 0.3% to 5.8 ± 0.3%, while SBP was also dropped from 130.0 ±

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37.2 mmHg to 119.7 ± 9.4 mmHg. However, the degree of the decrease in HbA1c levels was not significantly correlated with that of SBP (r = 0.24). In conclusion, the present findings suggest that sitagliptin lowers SBP without reducing BMI, independent of the blood glucose reduction. The hypotensive effect is apparent with the alternate-day regimen of sitagliptin at a lower dose compared to the everyday medication.

3. DPP-4 INHIBITOR SITAGLIPTIN ON GLYCEMIC CONTROL

To examine the efficacy and safety of once-daily oral sitagliptin as monotherapy in patients with type 2 diabetes.In a randomized, double-blind, placebo-controlled study, 741 patients (baseline HbA(1c) [A1C] 8.0%) were randomized to sitagliptin 100 or 200 mg or placebo for 24 weeks. Sitagliptin 100 and 200 mg produced significant (P < 0.001) placebo-subtracted reductions in A1C (-0.79 and -0.94%, respectively) and fasting plasma glucose (-1.0 mmol/l [-17.1 mg/dl] and -1.2 mmol/l [-21.3 mg/dl], respectively). Patients with baseline A1C >or=9% had greater reductions in placebo-subtracted A1C with sitagliptin 100 and 200 mg (-1.52 and -1.50%, respectively) than those with baseline A1C <8% (-0.57 and -0.65%) or >or=8 to <9.0% (-0.80 and -1.13%, respectively). In a meal tolerance test, sitagliptin 100 and 200 mg significantly decreased 2-h postprandial glucose (PPG) (placebo-subtracted PPG -2.6 mmol/l [-46.7 mg/dl] and -3.0 mmol/l [-54.1 mg/dl], respectively). Results for the above key efficacy parameters were not significantly different between sitagliptin doses. Homeostasis model assessment of beta-cell function and proinsulin-to-insulin ratio improved with sitagliptin. The incidence of hypoglycemia was similar, and overall gastrointestinal adverse experiences were slightly higher with sitagliptin. No meaningful body weight changes from baseline were observed with sitagliptin 100 (-0.2 kg) or 200 mg (-0.1 kg). The body weight change with placebo (-1.1 kg) was significantly (P < 0.01) different from that observed with sitagliptin. In this 24-week study, once-daily sitagliptin monotherapy improved glycemic control in the fasting and postprandial states, improved measures of beta-cell function, and was well tolerated in patients with type 2 diabetes.

4. DPP-4 INHIBITOR SITAGLIPTIN PROTECTS ENDOTHELIAL FUNCTION

Sitagliptin, a selective dipeptidyl peptidase 4 inhibitor, inhibits the inactivation and degradation of glucagon like peptide 1 (GLP-1), which is used for the treatment of type 2 diabetes mellitus. However, little is known about the role of GLP-1 in hypertension. This study investigated whether the activation of GLP-1 signaling protects endothelial function in hypertension. Two-week sitagliptin treatment (10 mg/kg per day, oral gavage) improved endothelium-dependent relaxation in renal arteries, restored renal blood flow, and reduced systolic blood pressure in spontaneously hypertensive rats. In vivo sitagliptin treatment elevated GLP-1 and GLP-1 receptor expressions, increased cAMP level, and subsequently activated protein kinase A, liver kinase B1, AMP-activated protein kinase-α and endothelial NO synthase in spontaneously hypertensive rat renal arteries. Inhibition of GLP-1 receptor, adenylyl cyclase, protein kinase A, AMP-activated protein kinase-α, or NO synthase reversed the protective effects of sitagliptin. We also demonstrate that GLP-1 receptor agonist exendin 4 in vitro treatment had similar vasoprotective effects in spontaneously hypertensive rat renal arteries and increased NO production in spontaneously hypertensive rat aortic endothelial cells. Studies using transient expressions of wild-type and dominant-negative AMP-activated protein kinase-α2 support the critical role of AMP-activated protein kinase-α in mediating the effect of GLP-1 in endothelial cells. Ex vivo exendin 4 treatment also improved endothelial function of renal arteries from hypertensive patients. Our results elucidate that upregulation of GLP-1 and related agents improve endothelial function in hypertension by restoring NO bioavailability, suggesting that GLP-1 signaling could be a therapeutic target in hypertension-related vascular events.

5. CONCLUSION

The other way to utilize GLP-1 effects in type 2 diabetes is the direct inhibition of DPP-4 by orally active substances. Sitagliptin (Januvia®, Merck Pharmaceuticals, Whitehouse Station NJ, USA) is a highly selective DPP-4 inhibitor that has been approved for type 2 diabetes therapy. Other DPP-4 inhibitors are also in development or close to approval, such as vildagliptin (Galvus®, Novartis Pharmaceuticals, Basel, Switzerland).

REFERENCE

1. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Research and Clinical Practice.* 2010, 87(1), 4–14
2. Sturm R. Stemming the global obesity epidemic: what can we learn from data about social and economic trends? *Public Health*. 2008, 122(8), 739–746
3. Ray KK, Seshasai SRK, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet*. 2009, 373(9677), 1765–1772
4. Mannucci E, Monami M, Lamanna C, et al. Prevention of cardiovascular disease through glycemic control in type 2 diabetes, a meta-analysis of randomized clinical trials. *Nutrition, Metabolism and Cardiovascular Diseases*. 2009, 19(9), 604–612
5. Preumont V, Hermans MP, Brichard S, Buysschaert M. Six-month exenatide improves HOMA hyperbolic product in type 2 diabetic patients mostly by enhancing beta-cell function rather than insulin sensitivity. *Diabetes Metab*. 2010, 36(4), 293–8

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