Dipeptidyl Peptidase (DPP)-IV Inhibitor: A Novel Class of Oral Anti-hyperglycemic Agents

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Type 2 diabetes is a progressive, metabolic disorder characterised by two fundamental defects: insulin resistance at peripheral target tissues and pancreatic beta-cell dysfunction. Insulin sensitivity declines as an individual moves from normal to impaired glucose tolerance state. Pancreatic beta cells compensate by hyper-secretion of insulin in order to maintain normoglycaemia. Where pancreatic beta cells exhaust and the function of pancreatic beta cells deteriorates progressively, an individual progresses from the state of impaired fasting glucose or impaired glucose tolerance to frank diabetes1,2.

Despite good compliance to treatment, the glycaemic control of type 2 diabetes deteriorates progressively. Analysis from the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that after 3 years of longitudinal follow up, only 50% of the initial cohort could achieve the target haemoglobin A1c (HbA1c) control of <7% while the remaining 50% required the addition of a second drug for diabetes control. By the time of nine years, 75% of patients required multiple therapies to achieve the target HbA1c control3. Hence, new therapeutic agents are continuously being developed to help our diabetes population. Recent studies have shown that early intervention at pre-diabetes state4,5 and beta cell protection with insulin sensitisers6 may improve the prognosis of diabetes.

Dipeptidyl peptidase (DPP)-IV inhibitors, which act via enhancing the incretins, represent another new therapeutic approach to the treatment of type 2 diabetes. Glucagon-like peptide 1 (GLP-1) and glucose dependent insulinotropic peptide (GIP) account for the majority of incretin action7. GLP-1 is a gut hormone that plays a key role in glucose homeostasis via its incretin effect. GLP-1 is produced from the enteroendocrine L-cell of small intestine and is secreted in response to meal and nutrients (Table 1). It stimulates insulin release from the pancreatic islets in a glucose dependent manner. It restores the defective first and second phases of insulin response to glucose in type 2 diabetes patients8,9. Moreover, GLP-1 suppresses post-prandial glucagon release, delay gastric emptying and increase satiety10-12. In animal models, GLP-1 and its analogs are shown to stimulate beta-cell proliferation and differentiation. These may help in preserving the pancreatic beta cell mass and function, and thus have beneficial effect in the prognosis of type 2 diabetes13,14. However, GLP-1 has a very short half-life. It is rapidly degraded inside our body by the enzyme dipeptidyl peptidase (DPP)-IV. Therapeutic agents, that can block the DPP-IV enzyme (DPP-IV inhibitor), can increase the endogeneous GLP-1 level and thus enhances the incretin action.

Sitagliptin is a potent and highly selective DPP-IV inhibitor. It is the first from this novel class of oral anti-hyperglycaemic agent that has been approved by the United States (US) FDA in October 2006 for the treatment of type 2 diabetes. It can be used as a monotherapy or in combination with metformin or thiazolidinedione. Sitagliptin is orally active and can be administrated once daily. A single oral dose of Sitagliptin ≥ 100mg can inhibit plasma DPP-IV activity 80% over 24 hours of time15. By slowing incretin degradations, Sitagliptin increases meal-stimulated active GLP-1 level to two to threefold, leading to increase in insulin and C-peptide levels, reduction in plasma glucagon levels, reduction in post-prandial glucose excursion and better glycaemic control in type 2 diabetes patients16. A 24-week randomised, double-blinded, placebo-controlled study in type 2 diabetes patients demonstrated that Sitagliptin 100mg daily monotherapy improved fasting and postprandial glycaemic control, reduced HbA1c by 0.79% (p<0.001), improved beta-cell function, with neutral effect on body weight, similar incidence of hypoglycaemia, slightly higher overall gastrointestinal adverse experiences when compared with placebo. Patients with baseline HbA1c ≥ 9% had greater reductions in placebo-subtracted HbA1c (-1.52%) than those with baseline HbA1c <9%17. DPP-IV inhibitor had been shown to improve beta cell function in patients and animal models with type 2 diabetes18-21. In animal models, DPP-IV inhibitor can lead to beta cell neogenesis and survival22-23. Nonetheless, long term clinical studies are required to see whether similar beta cell effects are found in patients with type 2 diabetes. Vildagliptin is another DPP-IV inhibitor which acts via similar mechanism as Sitagliptin but has not yet been approved by US FDA.

In summary, DPP-IV inhibitors is a novel class of oral hypoglycaemic agent with potentials in improving pancreatic beta cell function and the clinical course of type 2 diabetes. More clinical trials are needed to explore their long-term clinical effects and their potential beneficial effects in human beta cell neogenesis and survival.

Table 1. Action of Glucagon-like peptide (GLP-1).

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<th>Action of GLP-1:</th>
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<tr>
<td>1. Stimulate insulin secretion in glucose-dependent manner.</td>
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<tr>
<td>2. Decrease glucagon secretion in glucose-dependent manner.</td>
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<td>3. Delay gastric emptying.</td>
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<td>4. Decrease appetite.</td>
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<td>5. Increase pancreatic beta cell mass.</td>
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References