FRESH FROM THE PIPELINE

Sitagliptin

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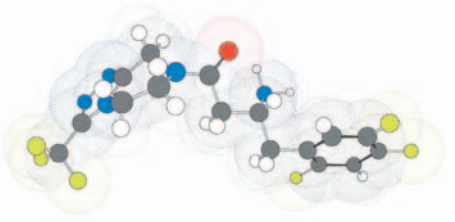


Sitagliptin

Sitagliptin phosphate (Januvia; Merck) was approved by the US FDA for the treatment of type 2 diabetes mellitus in October 2006. It is the first in a new class of drugs that inhibit the proteolytic activity of dipeptidyl peptidase-4, thereby potentiating the action of endogenous glucoregulatory peptides, known as incretins.

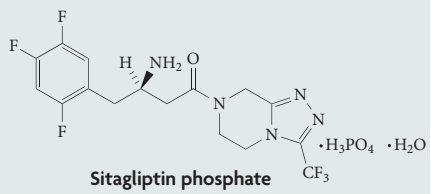
Tight glycaemic control is considered to be important in the therapy of type 2 diabetes mellitus (T2DM), but treatment with a single agent is not sufficient to achieve this for the majority of patients. So, there is a need for new antidiabetic agents with favourable side-effect profiles to use in combination therapy.

Basis of discovery

Advances in the understanding of the actions of endogenous glucoregulatory peptide hormones, known as incretins, have identified new therapeutic targets for T2DM. Two incretins — glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP1) — potentiate glucose-dependent insulin secretion from islet β-cells by activating specific G-protein-coupled receptors[1]. GLP1 also inhibits glucagon secretion and gastric emptying and induces a feeling of satiety, which leads to weight loss in the majority of treated subjects[1]. As incretin receptor activation is only coupled to stimulation of insulin secretion in the presence of elevated blood glucose[1], therapies that are based on potentiating endogenous incretin action should have a low risk of hypoglycaemia, which is a problem with several current therapies, such as the sulphonylureas.

However, although native GLP1(7–36) amide effectively lowers blood glucose, it is rapidly degraded by the ubiquitous serine protease dipeptidyl peptidase-4 (DPP4)[1]. One approach to combat this problem has been the development of long-acting degradation-resistant peptides that are subcutaneously injected[2]. In April 2005, exenatide (Byetta; Amylin), a peptidic GLP1 receptor agonist, was approved by the FDA for T2DM. An alternative strategy has focused on the inhibition of the proteolytic activity of DPP4 to prevent the degradation of GLP1 and GIP.

DPP4 is a complex molecule that exists as a membrane-spanning cell-anchored protein that is expressed on many cell types, and as a soluble form in the circulation; both forms have proteolytic activity[1]. Several lines of evidence have suggested that DPP4 is essential for the control of GLP1 bioactivity and glucose homeostasis. Importantly, small-molecule inhibitors of DPP4 prevented the *N*-terminal degradation of GLP1, and lowered blood glucose in preclinical studies[2]. Complementary experiments indicated that mice with a targeted disruption of the *DPP4* gene had increased plasma levels of GLP1 and GIP, enhanced glucose-stimulated insulin secretion and reduced glycaemic excursion following oral glucose challenge[3]. Proof-of-concept for the efficacy of DPP4 inhibitors as antidiabetic agents in humans was then reported using NVP DPP728, a first-generation small-molecule DPP4 inhibitor[4], which further encouraged the discovery and development of such agents, including sitagliptin[5].



Sitagliptin phosphate

7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl) butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate; $C_{16}H_{15}F_6N_5O{\cdot}H_3PO_4{\cdot}H_2O$; M_r = 523.32

Figure 1 | **Sitagliptin phosphate.**

Drug properties

Sitagliptin (FIG. 1) is an orally-bioavailable selective DPP4 inhibitor that was discovered through the optimization of a class of β-amino-acid-derived DPP4 inhibitors[5]. It lowers DPP4 activity in a sustained manner following once daily administration, preserves the circulating levels of intact GIP and GLP1 following meals in both acute and chronic studies and reduces blood glucose levels without significant increases in hypoglycaemia[6].

Clinical data

The safety and efficacy of sitagliptin as a monotherapy and in combination with existing antidiabetic agents was assessed in four randomized double-blind placebo-controlled clinical trials that involved more than 2,000 patients with T2DM[6–10]. Several measurements relevant to glycaemic control were evaluated, including the mean change from baseline in glycated haemoglobin (HbA_{1C}) levels — an indicator of average blood-sugar levels for the past 3–4 months.

Sitagliptin as a monotherapy at doses of either 100 or 200 mg daily significantly reduced HbA_{1C}, with few adverse events, and no significant increase in hypoglycaemia[7,8]. The extent of HbA_{1C} reduction was proportional to the starting HbA_{1C}, and no significant weight gain was observed in 24-week monotherapy studies. Sitagliptin reduced both fasting and postprandial glycaemia, in association with improvements in the proinsulin/insulin ratio and homeostatic model assessment of β-cell function (HOMA-B)[8].

For patients who did not achieve adequate glycaemic control on at least 1,500 mg per day of metformin (mean HbA_{1C} of 8%), the addition of sitagliptin 100 mg daily resulted in 47% of patients achieving a HbA_{1C} of <7%, compared with 18.3% of placebo-treated subjects[9]. The mean placebo-subtracted reduction in HbA_{1C} was 0.65%, and sitagliptin therapy was also associated with significant reductions in fasting glucose and increases in parameters of β-cell function. Sitagliptin has also been shown to be effective when combined with metformin as initial therapy for T2DM.

In 24-week studies of sitagliptin as an add-on therapy for patients not achieving adequate glycaemic control (mean HbA_{1C} ~8.1%) on pioglitazone (30 or 45 mg daily), sitagliptin at a dose of 100 mg daily produced a mean HbA_{1C} reduction of 0.7%, and significantly greater numbers of patients achieved a HbA_{1C} of <7% on sitagliptin relative to pioglitazone alone (45.4 versus 23%, respectively)[10]. Sitagliptin therapy was not associated with increased rates of hypoglycaemia or weight gain relative to patients treated with pioglitazone alone.

Indications

Sitagliptin is approved by the FDA as an adjunct to diet and exercise to improve glycaemic control in patients with T2DM, either as a monotherapy, or in combination with metformin or a peroxisome proliferator-activated receptor-γ agonist (for example, thiazolidinediones) when the single agent does not provide adequate glycaemic control[6]. ▸

ANALYSIS | TYPE 2 DIABETES MELLITUS

Analysing clinical issues for emerging therapies for T2DM is Daniel Drucker, Director of the Banting and Best Diabetes Centre and Professor of Medicine, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, University of Toronto, Canada.

Metformin is widely viewed as the initial drug of choice for the treatment of T2DM, owing to its 30-year track record, efficacy, safety and low cost. However, many physicians now advocate initiating therapy of T2DM with at least two drugs to obviate the monotherapy failure that accompanies prolonged metformin use in the majority of treated patients. There are now at least seven different classes of agents that can be used in combination with metformin, including sulphonylureas, glitinides, α-glucosidase inhibitors, thiazolidinediones, insulin (injected or inhaled), the GLP1R agonist exenatide and the DPP4 inhibitor sitagliptin.

So, how is the clinician to choose amongst these agents, when the ease of use, efficacy, safety, long-term durability and cost has to be balanced? Unfortunately, there is little information available from randomized-control trials that directly compare the efficacy of these different agents when added to metformin to answer this question. Insulin secretagogues, such as the sulphonylureas and glitinides, are inexpensive but are associated with weight gain and hypoglycaemia, which can be particularly problematic in elderly patients. The α-glucosidase inhibitors are effective and safe, but are frequently associated with gastrointestinal side effects that limit their tolerability. Thiazolidinediones improve insulin action with a low risk of hypoglycaemia and have appealing long-term durability, but the side effects of fluid retention and weight gain might be problematic for many patients. Exenatide produces comparable glycaemic control with weight loss versus weight gain seen with insulin in head-to-head studies[11]. However, the need for twice-daily injections and mild-to-moderate nausea might be challenging for some patients.

The available evidence suggests that metformin is more effective as monotherapy than either sitagliptin, or the related DPP4 inhibitor, vildagliptin. At present, there is no available data for head-to-head comparison of sitagliptin to alternative agents in combination with metformin for the treatment of T2DM not adequately controlled on metformin alone. There is also no long-term data available to inform patients and physicians about the likelihood of sitagliptin therapy maintaining sustained control of T2DM for prolonged periods of time. Furthermore, there is no data available for either exenatide or sitagliptin on the prevention of T2DM progression or cardiovascular outcomes.

As is the case with any new agent, the understanding of the adverse-event profile for sitagliptin is limited to the Phase III clinical data, and the long-term safety of prolonged DPP4 inhibition in patients with T2DM is unknown. Similarly, whether sitagliptin will prove to be effective for the prevention of T2DM in at-risk populations requires further study.

The past few years have witnessed considerable progress in the pharmacotherapy of T2DM, and the ease of use, favourable adverse-event profile and lack of hypoglycaemia or weight gain are attractive features for the new class of DPP4 inhibitors exemplified by sitagliptin. Additional studies are needed to define the long-term efficacy and safety of sitagliptin, and to determine its relative merit compared with the growing number of options now available for the treatment of T2DM.

Box 1 | Market for therapies for type 2 diabetes mellitus

Analysing the market for therapies for type 2 diabetes mellitus (T2DM) is Chris Easley, Engagement Manager, Product & Portfolio Development Practice, IMS Management Consulting, London, UK.

The rise in obesity is driving a rapid upward trend in diabetes prevalence, particularly in developed countries. More than 200 million adults have T2DM (with an estimated 70 million in the United States and Europe), and there is a high degree of under-diagnosis and sub-optimal treatment.

Various oral pharmacotherapeutic approaches exist to control blood sugar levels and thereby reduce co-morbidity and mortality associated with T2DM. However, current products are unable to prevent the decline in β-cell function, and disease progression leads many patients ultimately to require insulin injections. Sulphonylureas and metformin in monotherapy or in combination continue to be the mainstays of first- and second-line therapy; however, the newer thiazolidinedione class of drugs, which target peroxisome proliferator-activated receptors, represent the largest segment of the market by value, with nearly 80% market share in the United States and around 30% in Europe. The compound annual growth rate for the global oral antidiabetic market (excluding insulin) has been ~ 8% during the last 4 years.

Sitagliptin (Merck) was approved by the FDA in October 2006, and analysts predict peak worldwide sales of around US$1 billion in 2010, with 75% of sales coming from the United States. Novartis is following with its own DPP4 inhibitor, vildagliptin, which it expects the FDA to review in February 2007. Merck also plans an FDA filing in 2007 for a combination product of sitagliptin with metformin. Although an advance for the treatment of T2DM, the DPP4 inhibitors do not represent a breakthrough in glucose control. Uptake of the class will be greatest in the United States, whereas in Europe, usage will probably be limited to niche patient subgroups that have previously failed well-established — and inexpensive — therapies.

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Competing interests statement
D.D. declares competing financial interests: see web version for details.