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Review article

Incretin mimetics and enhancers: New insulin secretagogues for Type-2 diabetes

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Abstract

Hyperglycemia, obesity, insulin resistance, dyslipidemia and hypertension are interrelated cardiometabolic risk factors for the development of type-2 diabetes and metabolic syndrome. Prevalence of type-2 diabetes is growing at an alarming rate. Treatment target for type-2 diabetes is to keep daily glucose profile as close as possible to that of a non-diabetic person. Sulfonylureas, thiazolidinediones, meglitinides, biguanides and acarbose inhibitors are already being used in controlling glucose levels in type-2 diabetes. Mimicking or enhancing the actions of incretin is a new strategy which can help to control glucose levels in type-2 diabetics. This review discusses the incretin mimetics and enhancers, drug group with novel mechanism of actions; which were marketed recently or will be in market in near future. Exenatide and liraglutide are injectable glucagon-like peptide-1 receptor agonists, while vildagliptin and sitagliptin are oral dipeptidyl peptidase 4 inhibitors.

Key Words: Type-2 diabetes, Pharmacotherapy, Incretins, Exenatide

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Introduction

Type-2 diabetes is the most common metabolic disorder worldwide, and its prevalence is growing at an alarming rate in both developed and developing countries. This growth has been related to the increased prevalence of obesity. A cluster of interrelated cardio-metabolic risk factors is closely related to the development of type-2 diabetes and cardiovascular disease. Obesity, hyperglycemia and insulin resistance, dyslipidemia, inflammation, and hypertension represent interrelated therapeutic targets in the battle against the increasing prevalence of type-2 diabetes [1] The evidence, that obesity and diabetes is associated with risk of carcinoma has made the picture murkier. The most common type of diabetes mellitus, type-2, seems to be associated with liver and pancreas cancer and probably with colorectal cancer [2].

Treatment targets for type-2 diabetes include restoring blood glucose to normal levels so as to abolish diabetic symptoms; and the risk of acute and chronic metabolic complications. In a large scale study, a 1% reduction in HbA_{IC} resulted in 21% reduction in diabetic related deaths, 37% reduction in microvascular disease, 14% reduction in myocardial infarction and 21% reduction in all diabetes related end points [3].

Oral antidiabetic agents for type-2 diabetes already available in market include sulfonylureas (tolbutamide, chlorpropamide, glibenclamide, gliclazide, glipizide, glimepiride); biguanides (phenformin, metformin); thiazolidinediones (pioglitazone, rosiglitazone) meglitinides (repaglinide, nateglinide); alpha-glucosidase inhibitors (acarbose, miglitol, voglibose) and miscellaneous ones (aspartame, chromium picolinate, guargum, glucomannan), available either singly or as combinations [4].

With all these available options, still, sometimes glucose control is not maintained; and many patients ultimately have to put on insulin therapy. To have tighter glucose control and to obviate the need of insulin injections, new insulin secretagogues, which act through incretin patways have either been marketed or are in the development phase [5-8].

Incretin Pathways

Incretins, i.e glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are re-

leased from upper and lower bowel that augments glucose-dependent insulin secretion. This action is seen more with GLP-1. GLP-1 also reduces glucagon secretion, slows gastric emptying and decreases appetite; so ultimately reduces postprandial glucose rise and weight loss [9].

Incretins are readily degraded by enzyme dipeptidyl peptidase-4 (DPP-4) *in vivo*. So the blockade of incretin degradation increases their physiological actions, including the stimulation of insulin secretion and inhibition of glucagon release. By potentiating the actions of the incretins, DPP-4 inhibition can improve secretary functions in diabetics [10].

In type-2 diabetes, the secretion of GIP remains normal but the insulin response to it is impaired. GLP-1 concentrations are reduced in type-2 diabetes but the pancreatic response is relatively preserved. Using agonists to mimic the action of incretin, or inhibiting incretin metabolism to enhance the effect, are new strategies to treat type-2 diabetes [11].

Incretin mimetics and enhancers

Many new incretin mimetics and enhancers are in the pipeline; they have either been introduced recently or are undergoing late phase 3 trials or a New Drug Application (NDA) has been applied for. These drugs [5-8] are:

Glucagon-like Peptide-1 (GLP-1) analogues: Exenatide, Liraglutide, Albiglutide, Taspoglutide
Dipeptidyl Peptidase-4 (DPP-4) inhibitors: Alogliptin, Linagliptin, Saxagliptin, Sitagliptin, Vildagliptin

Incretin mimetics: GLP-1 analogues

GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4), so its potential as a drug is very limited. However, drugs which are synthetic agonists at the GLP-1 receptor resist cleavage by DPP-4 [12].

Exenatide

Exenatide is a 39-amino acid peptide, GLP-1 analogue and insulin secretagogue with gluco-regulatory effects. Exenatide is indicated for type-2 diabetic patients whose diabetes is not well-controlled by other oral medications. It enhances glucose-dependent insulin secretion by the pancreatic beta-cell, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying. It particularly decreases post-prandial glycemia [13].

Exenatide is administered as a subcutaneous injection (under the skin) of the abdomen, thigh, or arm, 30 to 60 minutes before the first and last meal of the day, from a pre-filled pen device. Exenatide pen contains sixty doses to be used in 30 days. The medicine is available in two doses: 5 μg and 10 μg. Treatment often begins with the 5 μg dosage, which is increased if adverse effects are not significant [13]. Long acting release formulation has also been studied and in a dose of 2mg/week, it has shown comparable response to twice daily regimen [5].

Exenatide is cleared by glomerular filtration and while no dose adjustment is needed for mild renal impairment, exenatide probably should not be used in patients with a creatinine clearance less than 30 mL/min or on dialysis. There have been no studies in patients with liver disease and the effects on human pregnancy are unknown [12].

Efficacy of exenatide in combination with oral hypoglycemic agents

Randomised placebo-controlled clinical trials have enrolled 1689 patients with suboptimally controlled type-2 diabetes despite treatment with metformin, sulfonylureas or thiazolidinediones. The metformin and/or sulfonylurea studies lasted 30 weeks and the thiazolidinedione study lasted 16 weeks. Patients were randomised to add placebo, low- (5 μg) or high-dose (10 μg) exenatide twice daily [14]. The mean effects of exenatide, in comparison to placebo, were:

- a reduction in glycated haemoglobin (HbA_{IC}) of approximately 0.6% with low dose and 1.0% with high dose
- a reduction in fasting plasma glucose of approximately 1.0 mmol/L with low dose and 1.4 mmol/L with high dose
- reductions in postprandial glucose of approximately 2.0 mmol/L with low dose and 3.0 mmol/L with high dose
- progressive weight loss during the trial period, with a reduction in body weight of approximately 0.8 kg with low dose and 1.4 kg with high dose.

A total of 974 patients opted to continue exenatide in uncontrolled open-label extensions to these trials. For 283 patients, follow-up lasted for two years. During these two years the HbA_{IC} reduction (approximately 1.0% from baseline) was sustained and weight loss continued (4.7 kg below baseline). Other statistically significant effects were increased high density lipoprotein cholesterol (0.12 mmol/L), decreased triglycerides (0.4 mmol/L) and decreased diastolic blood pressure (2.7 mmHg). The alanine transaminase concentration returned to normal in 39% of the patients who had elevated baseline concentrations [14]. This reduction probably reflects a decrease in liver inflammation in patients with non-alcoholic fatty liver disease.

The long-acting release formulation of exenatide has been used in a randomised placebo-controlled study of 45 pa-

tients with type 2 diabetes [15]. After 15 weeks of once-weekly subcutaneous injections the mean changes were:

- a reduction in HbA_{IC} of 1.4% to 1.7% from baseline (with 0.8 mg and 2.0 mg/week respectively) compared to a rise of 0.4% with placebo
- a reduction in fasting plasma glucose of 2.4 mmol/L and 2.2 mmol/L from baseline (with 0.8 mg and 2.0 mg/week respectively) compared to a rise of 1.0 mmol/L with placebo
- weight loss of 3.8 kg in the 2.0 mg/week arm, but no change in the 0.8 mg/week or placebo arms.

Efficacy of adding exenatide or insulin

In patients with suboptimally controlled diabetes despite maximal doses of metformin and a sulfonylurea, adding twice-daily exenatide was compared with adding once-daily insulin glargine [16]. After 26 weeks, HbA_{IC} had fallen by 1.1% in both groups. Exenatide reduced postprandial glucose more effectively and produced less nocturnal hypoglycemia than insulin, whereas insulin reduced fasting plasma glucose more than exenatide did. Body weight decreased with exenatide (2.3 kg) but increased (1.8 kg) with insulin glargine.

Similar results were found in a 52-week open-label study comparing the addition of exenatide with the addition of twice daily insulin aspart in patients with suboptimally controlled diabetes despite taking maximal doses of metformin and sulfonylurea [17]. The HbA_{IC} reduced by approximately 1% and fasting plasma glucose by approximately 1.7mmol/L in both groups. Exenatide produced a greater reduction in postprandial glucose and caused weight loss, whereas the patients given insulin gained weight (between-group difference 5.4 kg).

Safety and tolerability

The main side effects of exenatide use are gastrointestinal in nature, including acid or sour stomach, belching, diarrhoea, heartburn, indigestion, nausea, and vomiting; exenatide is therefore not meant for people with severe gastrointestinal disease. Other side effects include dizziness, headache, and feeling jittery. Few cases of pancreatitis were reported, so FDA has issued a statuary warning [13].

In an open label randomized controlled trial of 551 patients, exenatide treatment for 26 weeks was associated with 2.3 kg weight loss; however, gastrointestinal symptoms were more common in the exenatide group, including nausea (57.1%), vomiting (17.4%) and diarrhea (8.5%). For most patients, the nausea is mild to moderate and goes away entirely after a few days or weeks [16].

It is evident that one obvious advantage with exenatide is weight loss during treatment, which is seen only with other two antidiabetic drugs i.e. metformin and acarbose, but one obvious disadvantage is that it has to be injected.

Liraglutide

Liraglutide is long acting GLP-1 analogue that awaits FDA and EMEA (European Medical Agency) approval to be used in type 2 diabetes as once daily subcutaneous injection, [18] but as on April 2, 2009 FDA advisory panel has expressed serious concern that the drug causes thyroid tumors.

Efficacy of liraglutide in combination with oral hypoglycemic agents

In a randomized, double-blind, double-dummy, active-control, 5-armed parallel, multisite, multinational (21 countries) 26 week trial comparing the effectiveness of liraglutide (0.6, 1.2, or 1.8 mg/day) vs an active comparator, rosiglitazone (4 mg/day), or placebo in patients with type 2 diabetes inadequately controlled on a sulphonylurea (glimepiride 2-4 mg/day), involving 1041 patients, randomized to either liraglutide (n = 233, 228, 234 for 0.6, 1.2, or 1.8 mg), rosiglitazone (n = 232), or placebo (n = 114) following 2 weeks of glimepiride titration [19]; the mean effects achieved were::

- a reduction in glycated haemoglobin (HbA_{IC}) of approximately 1.1% with 1.2 and 1.8 mg dose, 0.6% with 0.6mg dose and 0.4% with rosiglitazone (a increase of 0.2% was seen in placebo group)
- a reduction in fasting plasma glucose by 1.6 mmol/L with 1.2 and 1.8mg dose compared to 1.0mmol/L decrease with rosiglitazone
- a reduction in post prandial plasma glucose by 2.5-2.7 mmol/L with 1.2 and 1.8 mg liraglutide compared to 1.8 and 0.4 mmol/L with rosiglitazone and placebo respectively
- weight reduction was seen with 1.8 mg liraglutide dose (0.2kg) only

In another 26-week, double-blind, double-dummy, placebo and active-controlled, parallel-group trial, 1,091 subjects were randomly assigned (2:2:2:1:2) to once-daily liraglutide (0.6, 1.2, or 1.8 mg/day injected subcutaneously), to placebo, or to glimepiride (4 mg once daily). All treatments were in combination therapy with metformin (1g twice daily) [20]. The mean effects were:

- a reduction in HbA_{IC} of approximately 1.0% with 1.2, 1.8 mg liraglutide and with glimepiride, 0.7% with 0.6 mg liraglutide and a increase of 0.1% with placebo

- a reduction in body weight in all liraglutide groups (1.8-2.8 kg) compared with an increase in the glimepiride group (1.0 kg)

LEAD-3 was a 52-week, randomozed, multicentric trial which compared the efficacy and safety of two doses of liraglutide (1.2 and 1.8 mg once daily) to glimepiride (8 mg once daily) [18]. Liraglutide provided substantial improvement in glucose control from baseline and statistically significant better glucose control than glimepiride. In addition, there was significant weight loss, as compared to weight gain with glimepiride, and significantly greater reduction in systolic blood pressure with both liraglutide groups compared to glimepiride.

In another 26-week, double-blind, placebo-controlled, parallel-group trial 533 subjects (1:1:1) were randomized to once-daily liraglutide (1.2 or 1.8 mg) or placebo in combination with metformin (1 g twice daily) and rosiglitazone (4 mg twice daily) [21]. Mean effects seen were:

- a reduction in HbA_{IC} of 1.5% with 1.2 and 1.8 mg liraglutide as compared to 0.5% for placebo
- a reduction in fasting plasma glucose by 40, 44 and 8 mg/dl for 1.2, 1.8 liraglutide and placebo respectively
- a decrease of 47, 49 and 14 mg/dl in post prandial glucose for 1.2, 1.8mg liraglutide and placebo respectively
- weight reduction with 1.2 and 1.8 mg liraglutide (1.0 and 2.0 respectively)
- a decrease of 6.7, 5.6 and 1.1 mmHg in systolic blood pressure in three groups respectively

Safety and tolerability

The most common adverse events seen with liraglutide are nausea, diarrhea, and vomiting, and most are short-term and mild or moderate in severity [18]. In LEAD-1, the main adverse events for all treatments were minor hypoglycaemia (<10%), nausea (<11%), vomiting (<5%) and diarrhoea (<8%) [19]. Gastrointestinal symptoms, that's too nausea is the most common reported adverse effects with liraglutide [20, 21].

Other GLP-1 analogues

Albiglutide, another GLP-1 analogue is a novel dipeptidyl peptidase-4-resistant glucagon-like peptide-1 dimer fused to human albumin designed to have sustained efficacy in type 2 diabetics. It is still under investigation. Its half life ranges from 6-7 days, so weekly injections can be given [6]. Effects of albiglutide were assessed in a single-blind dose-escalation study, involving 54 type-2 diabetic patients randomized to receive placebo or 9, 16, or 32 mg albiglutide on day 1 and 8. In a complementary study, 46 subjects were randomized to a single dose (16 or 64 mg) of albiglutide to the arm, leg, or abdomen. In 32 mg dose cohort, placebo-adjusted fasting plasma glucose decreased by 26.7 and 50.7 mg/dl on day 2 and 9, respectively. Postprandial glucose was also reduced. No hypoglycemic episodes were detected in the albiglutide cohorts [22]. Most common adverse effects seen with Albiglutide are headache and nausea [6, 22].

Another GLP-1 analogue under investigation is taspoglutide, which is to be used in a once-weekly dose. In a randomized control trial taspoglutide has shown preliminary efficacy in patients with type-2 diabetes who failed to obtain glycemic control despite 1,500 mg metformin daily [23]. Significant weight loss was also seen with taspoglutide. Although the number of patients enrolled in each arm (n=50) was quite small and the effects of taspoglutide were not dose dependent; yet the possibility of development of a drug which can be given once every two weeks do raises expectations.

Present status of GLP-1 analogues

The American Diabetes Association (ADA) released a revised consensus statement and treatment algorithm for the medical management of patients with type 2 diabetes in early 2009 [24]. A key revision to these guidelines is a recommendation to treat some patients with new medications, such as the glucagon-like peptide (GLP-1) receptor agonists. The two settings where exenatide is particularly recommended are:

- If hypoglycemia is particularly undesirable (e.g., in patients who have hazardous jobs)
- If promotion of weight loss is a major consideration and the HbA_{IC} level is close to target (<8.0%)

Incretin enhancers: DPP-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4) is the major enzyme responsible for degrading the incretins *in vivo*. So the blockade of incretin degradation increases their physiological actions, including the stimulation of insulin secretion and inhibition of gastric emptying. Incretins (GIP & GLP-1) also have powerful effects on beta-cell differentation, mitogenesis and survival. By potentiating these pleiotropic actions of the incretins, DPP-4 inhibition can therefore preserve beta-cell mass and improve secretory function in diabetics [10].

Sitagliptin

The first agent of this class, sitagliptin, (marketed under trade name Januvia) was approved by the FDA in October 2006, for use in addition to diet and exercise to improve blood sugar levels in patients with type-2 diabetes, alone or in combination with two other commonly prescribed oral diabetes medications, metformin or a PPAR-agonist,

when either of these drugs alone, along with diet and exercise, don't provide adequate blood sugar control [25].

Efficacy of sitagliptin as monotherapy or as add-on therapy

The trials of sitagliptin included 6315 people with type-2 diabetes and mostly ran for 24 weeks (range 12–52 weeks) [12]. Doses ranged from 10 mg to 200 mg/day with 100 mg/day the most common dose. The mean effects of sitagliptin 100 mg/day monotherapy when compared to placebo were:

- a reduction in HbA_{IC} of 0.8%
- a placebo-adjusted reduction in fasting plasma glucose of 1.1 mmol/L
- a reduction in 2-hour postprandial plasma glucose of 3.2 mmol/L (range 2.6–4.5 mmol/L)
- no significant weight change

When used as add-on therapy to metformin, sitagliptin 100 mg reduced HbA_{IC} by 0.7% and fasting plasma glucose by 1.5 mmol/L; significantly more than placebo. Adding sitagliptin to metformin was not inferior to adding glipizide to metformin. Compared to placebo, adding sitagliptin to pioglitazone treatment decreased HbA_{IC} by 0.7% and fasting plasma glucose by 1 mmol/L. When added to glimepiride, sitagliptin 100 mg reduced HbA_{IC} by 0.89% and by 0.6% when added to glimepiride plus metformin [12].

Vildagliptin

Vildagliptin (trade name Galvus) is another oral antidiabetic drug which is a DPP-4 inhibitor. The Food and Drug Administration had demanded additional clinical data before it could approve vildagliptin. While the drug is still not approved for use in the US, it has been approved by EMEA for use within the EU [26].

Efficacy of vildagliptin as monotherapy or as add-on therapy

The published randomised controlled trials of vildagliptin as monotherapy or add-on therapy enrolled 5165 patients with type-2 diabetes. Most trials ran for 24 weeks (range 12–52 weeks) [11]. The mean effects of daily vildagliptin monotherapy when compared to placebo were:

- a reduction in HbA_{IC} of 0.6% with vildagliptin 50 mg/day and 0.7% with vildagliptin 100 mg
- a reduction of fasting plasma glucose of approximately 0.9 mmol/L with vildagliptin 50 mg and 1 mmol/L with vildagliptin 100 mg
- a placebo-adjusted reduction in 4-hour postprandial plasma glucose of 1.5 mmol/L with 50 mg and 0.9 mmol/L with 100 mg
- no significant reduction in weight

When used as add-on therapy to metformin, vildagliptin reduced HbA_{IC} significantly when compared to placebo (by 0.7% with 50 mg and 1.1% with 100 mg). Daily doses also significantly reduced fasting plasma glucose (by 1 mmol/L with 50 mg and 1.5 mmol/L with 100 mg vildagliptin). When vildagliptin was added to pioglitazone treatment, combination therapy was significantly more efficacious in improving glycaemic control than either drug alone. The combination decreased HbA_{IC} by 0.7% (with 100 mg vildagliptin).

Safety and tolerability of sitagliptin and vildagliptin

The collective data show that vildagliptin and sitagliptin are well tolerated, with a low incidence of gastrointestinal effects or hypoglycaemia [11]. Most common side effects seen with sitagliptin, in clinical studies were upper respiratory tract infection, sore throat, and diarrhea [26].

Although extensive long-term, pre-clinical studies of the major DPP-4 inhibitors have failed to show any evidence of potential to cause tumors in laboratory animals, there was one *in-vitro* study that has raised some questions [27]. In theory, DPP-4 inhibitors may allow some cancers to progress, since DPP-4 appears to work as a suppressor in the development of cancer and tumors [27, 28, 29].

Other DPP-4 inhibitors

Other drugs in this class are saxagliptin, linagliptin and alogliptin, which are under development. AstraZeneca has submitted NDA for saxagliptin under trade name Onglyza to FDA and EMEA for approval [30]. Similarly, Takeda had submitted a NDA for alogliptin to the FDA, after positive results from Phase III clinical studies, [31] but in complete response letter, FDA has rejected the NDA as of now and has asked the company to conduct an additional cardiovascular safety trial that satisfies the December 2008 FDA Guidance [32].

Present status of DPP-4 inhibitors

The UK's National Institute of Clinical Excellence (NICE), the country's healthcare cost-effectiveness watchdog has issued new guidelines for the treatment of type-2 diabetes. NICE recommended the use of DPP-4 inhibitors, which include Merck's Januvia and Novartis' Galvus, for patients with type 2 diabetes if normal therapies do not work. NICE recommended that the DPP-4 therapies should be considered as a second-line therapy in patients who have side effects from metformin and sulfonylureas,

or who cannot be treated with insulin alongside these drugs [33].

Conclusion

Some of incretin mimetics and enhancers have already been approved like exenatide, sitagliptin, vildagliptin (only in EU); while questions have been raised on the safety issue regarding many new compounds being developed to counter type 2 diabetes and FDA has asked for additional clinical trial data. Never the less, these agents provide novel therapeutic mechanisms for controlling type 2 diabetes. So, let's keep our fingers crossed!!

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