

Position of Incretin Agents in the Traitement of Type 2 Diabetes Mellitus: Literature Review

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Abstract

Type 2 diabetes is a chronic and progressive pathology that requires monitoring and supervision for life, its management is difficult and requires continuous efforts with essential therapeutic scaling for the maintaining good glycemic balance.

Incretin agents are a new class of drugs that enriches the medical arsenal already available to treat type 2 diabetes; they represent a promising therapeutic option, because they do not cause hypoglycemia while having a beneficial or neutral effect on weight or even a reduction in cardiovascular risk.

Through this literature review, we will explain the place of incretin agents in the management of type 2 diabetes and their interest.

Keywords: Incretin mimetic; GLP1 analogues; DPP4 inhibitors; Type 2 diabetes

Introduction

Type 2 diabetes results from the progressive alteration of the endocrine function (insulin secretory) of the pancreatic beta cells as well as pancreatic endocrine inability to compensate peripheral insulin resistance.

It is a chronic and progressive pathology that requires a lifetime monitoring and surveillance with a therapeutic scaling, regarding the drug therapy.

Incretins are a new class of drugs that enriches the therapeutic arsenal already available to treat type 2 diabetes which is not fully satisfactory because it does not affect weight loss nor improves β cells function.

Incretins are a promising therapeutic option because they improve glycemic control, induce weight loss of about 2-3 kg/year and offer the hope of a stabilization or improvement of β cells function by promoting proliferation and inhibiting apoptosis of β cells.

Definition

Incretin are peptide hormones that potentiate insulin secretion in a glucose-dependent manner, they are released from the endocrine cells of the intestinal epithelium during nutrients passage.

There are two types of hormones:

- The Glucose-Dependent Insulinotropic Polypeptide (GIP)
- Glucagon-Like Peptide-1 (GLP-1) [1].

The incretin effect is the potentiation of insulin response during the oral glucose administration rather than intravenously, despite the

reproduction, of a controlled glycemic excursion of identical amplitude, this phenomenon is due to the potentiation of insulin secretion by the "incretin" at mealtimes [1].

Background

In 1906, Moore suggested that some factors produced by the intestinal mucosa in response to ingestion of nutrients can stimulate insulin secretion; the term "incretin" is used to describe these intestinal factors. This effect is about 50 to 70% of insulin secreted in a situation of nutrient absorption.

In 1973: The first incretin has been isolated from extracts of pig intestines and was named Gastric Inhibitory Polypeptide (GIP).

In 1984: Discovery of a second incretin called Glucagon Like Peptide 1 (GLP 1) after cloning and sequencing of the proglucagon gene.

Physiology

Insulin concentration was more important after oral administration of glucose than after intravenous administration, which highlights the specific contribution of incretin in insulin response.

The first identified incretin, GIP (glucose-dependent insulinotropic polypeptide) is produced by K-cells of the proximal intestine as the second, and GLP-1 (glucagon-like peptide-1) is secreted by the L-cells of the ileum and colon.

*Effects of GLP1:

- Stimulation of insulin secretion by glucose-dependent manner, indeed incretin secretion is inhibited when blood glucose drops below 0.55g/l.

- The GLP1 inhibits the effects of glucagon directly by inhibiting glucagon secretion by the pancreatic α -cells and indirectly via insulin secretion.

- Slow gastric emptying which helps reduce the immediate postprandial hyperglycemia.

- Central anorectic effect, the GLP1 increases satiety via the GLP-1R receptors in the CNS which modify the activity of neuronal circuits controlling food intake.

- Protective effects on B-cell islets of pancreatic Langerhans (antiapoptotic effect) and stimulates the differentiation and maturation of functional B-cell.

- On the cardiac level, GLP1 improves myocardial function and the systolic ejection and decreases the diastolic pressure of the RV in models of heart failure with a protective cardio action waning of a myocardial ischemic event.

Incretin's Pathogenesis in Type 2 Diabetes

In type 2 diabetes, "incretin effect" is altered; the insulinotropic activity of GLP-1 is preserved only this one is reduced.

Preserving the effectiveness of GLP-1 in type 2 diabetes explains why this hormone is at the origin of a new therapeutic class and considering its various actions, it is a good candidate for the treatment of type 2 diabetes. Thus, a new therapeutic target was defined in Type 2 diabetes which is the entero-insular axis and gastrointestinal hormones.

Several pharmacological strategies have been explored and two therapeutic classes have emerged; GLP-1 analogues of resistant to DPP4 injectable products kind of substitution of GLP1 hormone and DPP4 inhibitors or gliptins orally to maintain strong concentration of endogenous GLP1 this by inhibiting its degradation by the enzyme DPP4 [1].

Data from the literature confirm the promising nature of these two therapeutic classes with a substantial advantage of analogues on weight control, whereas DPP4 inhibitors have a better safety profile. In addition, their association with existing antidiabetic drugs, even in situations of failure of the latter seems to be very advantageous. However, questions about the effectiveness and safety especially during long-term of these drugs are still being laid, and it remains to better define their role in the therapeutic strategy for type -2 diabetes [1].

Glp1 Agonists or Glp1 Analogues

Several molecules have been developed. We quote Exenatide (Byetta), the Exenatide LAR and Liraglutide (Victoza).

They lead to a reduction in HbA1c of approximately 1 to 1.5%, comparable to that which can be observed when switching to insulin in patients who failed to oral therapy, with benefits in terms of weight loss estimated at 2-3 kg with an average total loss up to 6 kg with a beneficial effect on blood pressure, improvement markers of hepatic steatosis and lipid profile.

The most common side effects are gastrointestinal (nausea, vomiting), with a reported risk of acute pancreatitis but remains controversial.

These molecules are used with caution in case of renal insufficiency and are counter-indicated when the clearance is < 30 ml.

DDP4 Inhibitors

The DPP-4 inhibitors, reduce the degradation endogenous GLP-1 by the inhibition of the DPP-4 and extend thus the half-life of the endogenous GLP-1.

Several molecules have been developed to date: Sitagliptin (Januvia*), vildagliptin (Galvus*) Linagliptin (Trajenta*), Saxagliptin (Onglyza*) [1].

Monotherapy: several placebo-controlled trials have been done, period of 18 -24 weeks at of 100-200 mg/day doses: mean decrease in HbA1c of approximately 0.7% and significant improvement in blood glucose pre and postprandial and beta cell function [2].

A phase 3 study (P049 study) randomized, double-blind, mono therapy Sitagliptin vs. Metformin in 1050 T2DM patients: after 24 weeks of treatment, the difference between Sitagliptin and Metformin in terms of rate reduction HbA1c was 0.14% showing non-inferiority of Sitagliptin/Metformin [3].

In bitherapy in combination with Metformin for 24 weeks in patients uncontrolled by the latter, the Sitagliptin 100 mg/day achieved: a further decrease of 0.65% in HbA1c associated with a better glucose control pre-and postprandial and a better beta cell function [1].

The Vildagliptin has a good efficacy profile and job security in T2D patients beyond 65 years [4].

Thus gliptins allow a control of postprandial blood glucose and fasting and a reduction of HbA1c ranging from 0.6 to 1.1%, with an average of 0.7% and more if the HbA1c in the departure is greater than 9 or 10% with an anti-hyperglycaemic Action comparable to Sulfamides or Pioglitazone when combined with Metformin.

They have the advantage of being orally bioavailable and to be devoid of side effects such as nausea with a neutral effect on weight without weight gain and without hypoglycemia [5].

It is reported as side effects, a tendency to upper respiratory infections with cases of pancreatitis.

However, despite their good tolerance, questions remain unanswered, particularly those concerning the total selectivity of these drugs for DPP4 enzyme? It is an adequate retreat to widespread use that would give answers [6].

Position of Incretins in the Treatment of Type 2 Diabetes?

The treatment of diabetes, imposes two requirements; early intensification of treatment taking into account the concept of glycemic memory of tissues and prevention of hypoglycemia that should not be underestimated, incretins are this new useful therapeutic class to reconcile these two requirements.

Ddp4 Inhibitors in Initial Monotherapy

They probably do not replace Metformin, except in case of intolerance or contraindications that remain quite limited.

All advocates of Metformin: efficacy, tolerability, weight neutrality, absence of hypoglycemic risk and, in addition, high level of evidence in the UKPDS.

DDP4 Inhibitors in Bitherapy

The Metformin-DDP4 inhibitors, association is interesting in moderately hyperglycemic patients especially the recommendation to introduce a bitherapy from an HbA1c>6.5% rate exposed to a risk of hypoglycemia during the addition of Sulphamide or Glinide.

However, it is unclear whether this association is superior to conventional associations in case of high starting hyperglycemia.

GLP1 Analogues

Their future looks promising, especially if the number of injections is reduced (eg: weekly) and if the safety and durability of their effects are confirmed in the long term [4].

Type 2 Diabetes: Algorithm of Treatment, When Introducing Incretins?

The recommendations of the ADA / EASD 2012 emphasize on the therapeutic approach focused on patient, it must be adjusted according to the individual characteristics as the objectives for each patient [7].

Criteria of therapeutic choice in type 2 diabetes has been proposed, and in case of risk of hypoglycemia it is preferred to add Metformin, Incretins, Acarbose or Pioglitazone, however, if the patient is obese, it is preferred to introduce incretin (GLP-1 analogues if the aim is a weight loss or gliptines and acarbose for weight neutrality), and finally if the cost of treatment is our concern, sulfonamides seem to be the less expensive therapeutic class [7].

The action to be taken would be as recommended by the ADA / EASD 2012 as follows

First-line treatment: In monotherapy, Metformin and lifestyle and dietary rules, if Metformin contraindicated or poorly tolerated: sulfonamides, pioglitazone, DDP4 inhibitors are a good therapeutic option.

Second-line treatment: After failure of monotherapy, HbA1c>6.5 to 77%, we add a sulphamide, pioglitazone, or DPP4 inhibitors especially if important hypoglycemic risk.

Third-line treatment: Intensification of treatment after failure of bitherapy, or we opt for oral tritherapy (metformin, sulfamides, metformin or glitazone, sulfamide, DDP 4 inhibitors) or for tritherapy with an injectable treatment, insulin basal or GLP1 analogue, knowing that NICE (National institute for health and clinical excellence) recommends introducing these latter to patients with a BMI>35 kg/m² or with complications of obesity, for whom weight loss is to obtain.

Combination Therapy; Incretins-Insulin in Patients with Type 2 Diabetes Mellitus

It is an interesting and logical therapeutic approach for the treatment of type 2 diabetes, by the additive effect of lowering of

glycemia without risk of hypoglycemia as compared to insulin monotherapy, and a reduction of weight gain due to insulin therapy with possibility of continuing metformin [8].

The results of the combination of analogues insulin GLP1- basal are encouraging, they allow glycemic control improvement, limit weight gain may even induce weight loss and reduce insulin requirements; they are very interesting in patients poorly controlled with high doses of insulin and the consequences of those on weight excess.

However, combination of DDP4 inhibitors with basal insulin allows a reduction in HbA1c but without greater benefits on weight and hypoglycemia.

Possible Role of Incretins in the Reduction of Cardio-Vascular Risk

The low rate of GLP1 associated with obesity and insulin resistance and/or TD2 is considered a risk factor for the occurrence of cardiovascular events. It is also correlated with hypertriglyceridemia, hypo-and hypertension HDLémie, suggesting cardio protective role of incretins [9].

The GLP1 has potentially interesting cardiovascular effects, especially in the delicate patient or subject to risk, cardio protective role of GLP1 and the favorable effect on the failing heart, should be considered and the results of experimental data must be confirmed by more detailed clinical studies interesting analogues GLP1/inhibitors of DDP4.

Conclusion

The incretins are an effective therapeutic class in monotherapy or in combination with other anti-hyperglycemic, they do not cause hypoglycemia while having a positive or neutral effect on weight. They might even have other additional benefits, reduced cardiovascular risk; this underlines the particular interest of this innovative therapeutic approach in taking care of type 2 diabetes.

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