INCRETIN-BASED THERAPY IN THE MANAGEMENT OF TYPE 2 DIABETES

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Type 2 diabetes is a progressive disease due to reduced beta cell mass, which results in the failure of traditional treatment and the need for more intensive therapeutic measures to maintain a good glycaemic control. Within the last decade there was a preoccupation for developing new classes of drugs to achieve several goals: glycaemic control, weight loss and to preserve residual beta cell mass together with being safe, well tolerated and convenient to use. An important progress in this respect was the development of the incretin-based therapy. Incretins are gut hormones namely glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic peptide/gastric inhibitory peptide (GIP). These 2 incretins have different therapeutic potential. GLP-1 decreases appetite, delays gastric evacuation and inhibits glucagon secretion, while GIP affects minimally gastric emptying and does not affect glucagon secretion. GLP-1 is reduced in type 2 diabetes, while GIP is normal. For these reasons only GLP-1 was considered for developing a new class of drugs. GLP-1 is rapidly degraded by dipeptidyl peptidase 4 (DPP-4), with a half life of 2 min. Two alternative pathways have been thought to overcome this shortcoming: the development of GLP-1 analogs resistant to DPP-4 named incretin mimetics or the development of DPP-4 inhibitors.

Increased action of GLP-1 in patients with type 2 diabetes mellitus is a valuable therapeutic mean and the evidences support their use in patients in need of glycaemic and weight control together with a minimal risk of hypoglycaemia.

Key words: type 2 diabetes mellitus, incretin-mimetics, dipeptidyl peptidase -4 inhibitors.

INTRODUCTION

Pathogenesis of type 2 diabetes mellitus is due to the decrease of insulin secretion capacity as a consequence of a low beta cell mass in the presence of insulin-resistance. These events progress slowly to end in therapy failure, necessitating a more intensive therapy approach in order to maintain an optimal glycaemic control.

United Kingdom Prospective Diabetes Study (UKPDS) has established that at the time of diagnosis patients with type 2 diabetes mellitus present a reduction of beta cell function with 50%, which further decreases on average of 4% annually.1

The last decade research was preoccupied on development and license new classes of therapeutic means that cumulate both a hypoglycaemic effect and preservation of the residual beta cell mass together with safety, good tolerability and convenient use. In this respect an important progress in the therapy of type 2 diabetes mellitus has been the development of incretin-based therapy.

Incretins are gut hormones exemplified by glucagon-like peptide (GLP1) and glucose-dependent insulinotropic peptide/gastric inhibitory peptide (GIP). GLP-1 is synthesized by L cells present ubiquitarily at the gut level, with a maxim density in the distal ileum and colon, while GIP is produced in K cells from duodenum and proximal
Incretin plasma level is reduced during fasting and increases transiently after food ingestion. Incretins stimulate significantly insulin secretion and peptide C level mostly after oral glucose administration versus intravenous glucose. This particularity has been named incretin effect 3–5.

Studies showed a significant reduction of GLP1 after a mixed meal in patients with type 2 diabetes mellitus as compared to subjects with normal glucose tolerance. GLP1 secretion was assessed in 54 patients with type 2 diabetes mellitus, 33 subjects with normal glucose tolerance and 15 subjects with impaired glucose tolerance after a mixed meal. GLP-1 secretory response was significantly reduced in diabetics compared to normals. The patients with impaired glucose tolerance had a similar impairment of GLP-1 output as diabetics, though to a lower extend5.

The therapeutical potential of incretins is different: GLP-1 decreases appetite, delays gastric evacuation and inhibits glucagon secretion, while GIP as no effect on glucagon output and has a minimal effect on gastric emptying; GIP is normal in patients with type 2 diabetes, as opposed to GLP1 whose concentration is reduced. For these reasons only GLP1 has been chosen to develop a new therapeutic class of drugs6–8.

GLP-1 actions are mediated by a specific receptor present in pancreas, heart, kidney, lungs, thyroid C cells, pituitary, GI tract, peripheral and central nervous system (hypothalamus, hippocampus, cortex)9. Activation of the receptor by binding GLP-1 is followed by an increase in cAMP and intracellular calcium concentration that stimulates other signaling pathways dependent on protein kinase A, protein kinase C, phosphatidyl – inositol 3 kinase (PI-3K), mitogen activated protein kinase (MAPK) 8,10.

### PANCREATIC EFFECTS OF GLP-1

Within beta cells GLP-1 stimulates insulin secretion by stimulation of its gene transcription; the magnitude of this effect is dependent on the plasma glucose level, with a sudden onset at hyperglycaemic levels and an end when normal glycaemic levels are reached 11–17.

In experimental models on rodents and in cell cultures GLP-1 agonists have increased beta cell mass by stimulating cell proliferation via PI3K pathway 18 and by inhibition of apoptosis – mainly by increasing expression of antiapoptotic proteins and reducing expression of caspase 3.

Bcl-2 family comprises of pro- and anti-apoptotic proteins. Bcl-2 and Bcl-XL are anti-apoptotic members present in the mitochondrial membrane, while the pro-apoptotic proteins BAD or BAX reside in the cytosol. The latter act as sensors for stress signals. Cellular stress increases intracellular calcium which activates calcineurin phosphatase to subsequently dephosphorylate BAD and release it from the complex with protein 14-3-37. Now BAD can bind Bcl-2 from mitochondrial membrane, reducing its antiapoptotic function. Binding BAD on mitochondrial membrane induces pore formation and release of cytochrome C and other apoptotic molecules to form apoptosomes in the intermembranar space. Caspase cascade is activated to degrade cell DNA.

GLP-1 stimulates adenylate cyclase to generate cAMP that activates PKA. PKA subsequently phosphorylates BAD and favors its binding to 14-3- protein, thus retaining BAD within the cytosol 19–21.

There are controversies regarding the presence of GLP-1 receptors on the alpha pancreatic cells. Nevertheless GLP-1 administration induces glucagon suppression in a glucose-dependent manner 22, 23.

GLP-1 has also a stimulatory effect on somatostatin secretion in animal models24.

### EXTRAPANCREATIC EFFECTS OF GLP-1

GLP-1 delays gastric emptying which in turn reduces glycaemic postprandial increase and inhibits gastric secretion. This effect seems to be mediated via central and peripheral neuronal pathways and it is blunted by vagotomy27, 28.

Chronic pharmacologic administration of GLP-1 agonists induce anorexia and weight loss29, 30.

GLP-1 also can regulate growth and differentiation similar to a growth factor. GLP-1 activation was suggested to induce differentiation of exocrine pancreatic cells into an endocrine-like phenotype, increasing islet cell mass in humans and animal models26.
In muscle, adipose tissue and liver GLP-1 induces insulin-like effects on glycaemic homeostasis and lipid metabolism. There are still controversies with respect to the expression of GLP-1 receptors in these tissues and it has not been established yet whether GLP-1 acts independently, or its effects are secondary to the alterations in insulin, glucagon and somatostatin secretion. In experimental models GLP-1 administration was followed by an increase of glycogen synthesis and glucose oxidation secondary to activation of PI3K and MAPK pathways in muscle; in hepatocytes GLP-1 increases glycogen and reduces fatty acids synthesis and glucogenesis due to a decrease of phosphoenolpyruvatecarboxikinase and glucose-6-phosphatase.

GLP-1 receptors are also expressed in myocardium, endothelial cells and smooth muscle cells in the vessels, both in humans and in rodents. In experimental models GLP-1 has improved cardiac function, insulin sensitivity, myocardial glucose uptake and glycolysis and has reduced the size of myocardial infarction. In humans, GLP1 administration has improved left ventricular ejection fraction post myocardial infarction, regardless of the localization of the infarction or the history of diabetes. Ongoing studies will assess cardio protective effect of incretin-based therapy in patients with diabetes mellitus.

In animal models GLP-1 receptors are expressed in the pituitary and the hypothalamus, suggesting GLP-1 involvement in hypothalamo-pituitary axis regulation. Central administration of GLP-1 in animals has increased ACTH secretion and subsequently cortisol and corticosterone secretion. Other studies showed that GLP-1 stimulates the release of TSH and LH. The significance of these data in humans is not yet known.

Preclinical studies have revealed that C cells of the thyroid express GLP-1 receptors. In vitro activation of the receptor stimulates calcitonin secretion via cAMP and inhibits postprandial bone resorption. In rodents GLP-1 receptor stimulation induces C cell hyperplasia and medullary thyroid carcinoma (MTC) in rodents. Effect of GLP-1 on C cells in humans remain to be established.

GLP-1 is rapidly degraded by dipeptidyl peptidase 4 (DPP-4) that is a ubiquitous serine-peptidase that splits a dipeptidyl from the aminoterminal end of its target peptides. This results in a half life of GLP-1 of approximately 2 minutes. So the only way to use GLP-1 in therapy seemed to be continuous infusion, which is impractical for the long term therapy of type 2 diabetic patients. Later on have been identified two alternative ways to bypass DPP-4 degradation: development of GLP-1 analogs resistant to DPP-4 (incretin mimetics) and inhibition of DPP4 (DPP-4 inhibitors).

GLP-1 agonists are: exenatide and exenatide-LAR, liraglutide, taspoglutide, albiglutide and DPP inhibitors: sitagliptin, saxagliptin, vildagliptin, alogliptin, linagliptin.

**Efficacy of Incretin-Based Therapy**

Exenatide, the first incretin mimetic developed was incorporated into medical practice in 2005 and has been used in the therapy of type 2 diabetes mellitus in Romania since 2008. It has a structural homology of 53% with GLP1 and has a lasting effect of maximum 7 hours. Daily use consists of 2 subcutaneous injections prior to meals. Exenatide is cleared through renal excretion and therefore contraindicated in end stage renal failure.

Placebo controlled studies with exenatide added to the current antidiabetic medication have revealed a significant decrease in HbA1c of 1.1% in patients treated with exenatide. There was a significant, progressive, dose-dependent weight loss, without plateau until week 30, with a total reduction of 4.4% of initial weight in patients who participated in an open-labeled extension of the studies.

Liraglutide is a GLP-1 analogue with 97% homology with GLP1, with one aminoacid substitution and addition of palmitoyl (fatty acid with 16 carbon atoms) to a lysine residue. These alterations in structure result in an increase albumin affinity, increase half-life (up to 12 hours) and sparing of renal clearance. Liraglutide is administered once daily and has no contraindications in hepatic or renal failure. The efficacy of the therapy with liraglutide has been evaluated in randomized placebo controlled trials named LEAD (Liraglutide Effect and Action in Diabetes) that included over 4000 patients with type 2 diabetes mellitus.

LEAD 1 compared effects of liraglutide, rosiglitazone or placebo added to glimepiride therapy. The results showed that liraglutide 1.8 mg plus glimepiride have reduced HbA1c with 1.1%, significantly higher than rosiglitazone plus...
glimepiride (drop of HbA1c with 0.4%), while glimepiride alone was followed by an increase of HbA1c with 0.2%. The reductions in HbA1c were higher in patients with monotherapy prior to enrollment as compared to those with associated treatment.

LEAD 2 compared effects of metformin in association with liraglutide or glimepiride or placebo. Liraglutide 1.8 mg plus metformin have reduced HbA1c with 1%, similar to glimepiride plus metformin and significantly higher than metformin as monotherapy. As in LEAD 1, reductions in HbA1c were higher in patients with monotherapy prior to enrollment as compared to those with associated treatment.

Liraglutide in monotherapy (LEAD 3 study) in naive patients with type 2 diabetes has reduced HbA1c with 1.2-1.6%.

LEAD 4 and LEAD 5 studies have assessed effects of triple association liraglutide with metformin and rosiglitazone, or liraglutide in combination with metformin and glimepiride. Results showed a 1.5% reduction of HbA1c with the former combination, and 1.3% with the later.

LEAD 6 has compared the efficacy of liraglutide versus exenatide in association with metformin or sulphonylurea. The results had showed a significant reduction of HbA1c in patients treated with liraglutide versus placebo and exenatide.

The positive effects of liraglutide on weight loss observed in preclinical studies has been confirmed in LEAD studies.

In LEAD 1 liraglutide plus glimepiride have reduced body weight with a mean of 0.2 kg, while in LEAD 2 liraglutide plus metformin have dropped weight by 2.8 kg as compared with an average increase with 1 kg in patients treated with glimepiride plus metformin.

The LEAD studies have revealed that incretin-mimetics reduce HbA1c with 0.6%-1.5%, drop body weight and have a minimal risk of hypoglycaemia. The drawbacks of this therapy are the need for injections and the GI side effects, which are transient and get better in few weeks from therapy onset.

Inhibitors of DPP-4 have a good biodisponibility and significant antidiabetic effects. They have the advantage of oral administration, but no effect on body weight and have a reduced incidence of hypoglycaemia and no GI side effects.

Sitagliptin, the first inhibitor of DPP-4 has been approved in the United States in October 2006 and has been in use in Romania since 2008. Sitagliptin in monotherapy has been assessed in a double blind, placebo-controlled study over 24 weeks in 741 type 2 diabetic patients with an average history of 4.4 years since diagnosis. Patients had poorly controlled diabetes, with an average of HbA1c of 8%. 238 patients had been assessed on sitagliptin 100 mg/day, 250 on sitagliptin 200 mg/day and 253 on placebo (n=250). The drop in HbA1c has been statistically significant in patients with sitagliptin versus placebo. There were no significant differences in HbA1c reduction in patients on 100 or 200 mg/day. Sitagliptin in association with metformin, sulphonylurea and thiazolidindione have reduced HbA1c with 0.6-0.8% compared with placebo.

Vildagliptin efficacy has been assessed in several randomized placebo-controlled studies. Ferrannini and all have proved the non-inferiority of vildagliptin versus glimepiride in poorly controlled patients previously on metformin. Subjects have received vildagliptin (50 mg bid) or glimepirid (up to 6 mg/day, on average 4.5 mg daily) for 52 weeks. Vildagliptin in association with thiazolidindiones in poorly controlled patients has improved glycaemic profile.

In 2009 saxagliptin has been approved by European Medicines Agency for the treatment of type 2 diabetes in adults, in association with metformin, thiazolidindiones and sulphonylurea. The recommended dosage is 5 mg once daily. Saxagliptin has been assessed in clinical trials that included over 4000 patients with type 2 diabetes. In poorly controlled patients on metformin as monotherapy, association of saxagliptin (2.5 mg, 5 mg or 10 mg) has improved glycaemic control as compared with placebo. The percentage of patients who had attained HbA1c <7% after 24 weeks of treatment was significantly higher in saxagliptin compared to placebo. Association of saxagliptin 2.5 mg or 5 mg/day to gliburide or thiazolidindione has generated a significant reduction of HbA1c and basal glycaemia as compared to placebo.

Overall, studies results have showed that DDP-4 inhibitors drop HbA1c with 0.6%-1%, have a neutral effect on body weight and a reduced risk of hypoglycaemia. The advantages of this therapy over incretin-mimetics are oral administration and the lack of GI side effects.
SAFETY OF INCRETIN-BASED THERAPY

The most frequent side effects of GLP-1 agonists are of GI tract: nausea, vomiting, abdominal pain, diarrhea. These are transient and get better in few weeks from treatment onset.

Pancreatitis has been reported as a rare adverse event of exenatide, during postmarketing monitoring. An abstract of the first 30 cases of acute pancreatitis in patients treated with exenatide has been published in 2008. The authors have noticed in 90% of patients other predisposing factors for acute pancreatitis. The true relationship between exenatide therapy and incidence of acute pancreatitis is not yet established, as it is well known that patients with type 2 diabetes have an overall increased risk of pancreatitis of 3 fold than the general population.

Liraglutide manufacturer suggest a low incidence of acute pancreatitis.

Acute pancreatitis has been reported as an adverse event also during therapy with sitagliptin. 88 cases of acute pancreatitis have been recorded by FDA between October 2006 and February 2009. Due to the available data on acute pancreatitis and the association between these drugs and pancreatic metaplasia and chronic pancreatitis noticed during experimental studies, it is recommended to monitor closely pancreatic function in patients treated with GLP-1 of DPP-4 inhibitors.

Preclinical studies have showed that thyroid C cells express GLP-1 receptors whose activation induces C cell hyperplasia and MTC. Animal models develop spontaneously age-induced nodular hyperplasia of C cells frequently. Sporadic MCT has a frequency of 0.5-1%, in animal models, higher in males secondary to ageing. In humans, MCT represents 3-10% of thyroid cancer and approximately 75% are sporadic, with 25% being part of a multiple endocrine neoplasia or familial MTC, with autosomal dominant inheritance. Familial MCT is due to a mutation of RET proto-oncogene.

In 2009 the Regulatory Committee of FDA has communicated that preclinical toxicological studies with liraglutide have reported that C cell hyperplasia and MTC incidence increase with drug exposure. Single dose administration of liraglutide has increased the frequency of nodular lesions in C cells, but no MTC was reported. The present data suggest that MTC in rodents appears specifically to long acting GLP-1 agonist exposure, probably due to sustained stimulation of GLP-1 receptor. Clinical studies with liraglutide that monitored safety issues have revealed a small number of patients with an increase in calcitonin level during treatment. There have been reported few cases of papillary thyroid carcinoma during clinical development program of liraglutide, but data suggest these cannot be directly related to the GLP-1 agonist. Biological difference in C cells between human and rodents raise doubts about the utility of animal models in the study of human C cells during GLP-1 agonist therapy.

Due to DPP-4 expression on the surface of leucocytes, there is a concern regarding potential adverse events of DPP-4 inhibitors on immune system. There are reports of an increased incidence of upper respiratory airways’ infections in patients on treatment with DPP-4 inhibitors.

It is necessary to perform more long term safety studies to clarify the potential of pancreatic and thyroid impairment secondary to incretin-based therapy.

CONCLUSIONS

To increase action of GLP-1 in patients with type 2 diabetes is a valuable therapeutic tool and can be attained by using either a GLP-1 agonist as a subcutaneous injection or an oral DPP-4 inhibitor.

Studies have shown that incretin-mimetic therapy reduces HbA1c with 0.6%-1.5% on average and also drops weight and presents a lower risk of hypoglycaemia. Disadvantages of this therapy are the use of injections and gastrointestinal side effects, which are transient and get better in few weeks of the treatment onset.

DPP-4 inhibitors reduce HbA1c with 0.6%-1.1% on average, have a neutral effect on body weight and a reduced risk of hypoglycaemia. The advantages of this therapy are oral administration and lack of gastrointestinal side-effects.

Present evidences support the use of incretin-based therapies in patients who need a more efficient glycaemic and weight control with a minimal risk of hypoglycaemia.

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