Editorial
NEW MOLECULES IN DIABETES

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Without doubt, at present, diabetology is one of the most active fields of research with unexpected results of a surprising occurrence. As witnesses but as real participants in this scientific act as well, we feel obliged to permanently underline everything that is new and the benefits of every novelty both for the patient and from a financial point of view.

The novelty turned into reality this time is the incretinic therapy including two big therapeutic families: GLP-1 receptor agonists and DPP-4 inhibitors. At present we are already working for our patients with 5 and 10µg exenatide administered twice a day and with sitagliptine 100mg / day respectively.

We are currently discussing, researching and looking forward to new therapeutic families such as glucokinase activators, glucagon antagonists, sirtuins or SGLT2 inhibitors.

The most important incretinic hormone is the GLP-1 (glucagon-like peptide-1), which is exclusively responsible for the slowing down of the gastric evacuation, for the reduction of food supply and of glucagon secretion.

The other incretinic hormone is the GIP (glucagon-dependent insulinotropic polypeptide), which, together with the GLP-1, increases the insulin secretion and the proliferation of the β-cells reducing their apoptosis at the same time [1].

The clinical effects of the incretines are the loss in weight, the decrease of the insulin secretion and the improvement of the β-cells function.

The first GLP-1 analogue which appeared, the exenatide, was approved by the FDA in 2005 for human use in patients suffering from type 2 diabetes mellitus. It is a derivative of the exendin-4, which can be found in Gila Monster's saliva. Because this GLP-1 agonist is similar to the human GLP-1 only in a proportion of 53%, it will be less susceptible to be degraded in comparison to the human GLP-1, having a period of halving of 2.4 hours and not of two minutes as in the case of the human GLP-1.

Directions at present, accepted by all guides, are related to the therapy of patients in preinsulin phase, under therapy with oral antidiabetic agents which do not offer a sufficient metabolic balance. At present there are studies, but not validated yet, with GLP-1 agonist receptor with nondiabetic obese patients, monotherapy with drug naive patients with type 2 diabetes mellitus, in association with insulin or with DPP-4 inhibitors.

In the associations accepted at present we can notice a risk of hypoglycemia from slight to moderate when adding exenatide to sulfonylurea. In the associations with metformine or with tiazolidinedione, the risk of hypoglycemia is the same as the one witnessed in the case of exclusive or placebo exenatide. The exenatide is contraindicated in the final phase of a renal disease or in the case of a severe renal disorder.

The well-known secondary effects, which must be attentively monitored, are nausea and vomiting, while the hypoglycemia is present only in the associations exenatide-sulfonylurea [2].

Now, we can already discuss about exenatide long-acting release (LAR), administered once a week, which, according to the studies already completed, brings about encouraging results:

- the diminishing of the HbA1c is of over 1.7% in the exenatide LAR group in comparison to a 0.4% increase in the placebo group;
- fasting plasma glucose levels in the exenatide group decreased up to 43 mg/dl in the exenatide LAR groups, but increased 18 mg/dl in the placebo group;
- at the end of 30 weeks, the A1c decreased 1.9% in the exenatide LAR group, and 1.5% in the exenatide twice daily group (p=0.02);
- the reduction in fasting plasma glucose levels were greater in the exenatide LAR group (42 mg/dl vs. 25 mg/dl, respectively, p<0.001);

The DURATION program (Diabetes Therapy Utilization: Researching Changes in A1c, weight, and other Factors Through Intervention with Exenatide Once Weekly) has analysed in a comparative way the exenatide LAR and the exenatide, the sitagliptine, the pioglitazone, the glargine, the metformine and the liraglutide, respectively. (DURATION-6).

The liraglutide is an extremely recent GLP-1 agonist receptor which has a 97% similitude to the native GLP-1 which is administered once a day [3].

The program DURATION 1-5 has proved a superior glycemic control with exenatide LAR comparatively to the daily maximum intakes of exenatide, sitagliptine, pioglitazone or similarly to the control by glargine insulin. The exenatide LAR has proved a superior weight loss in comparison to the other comparators. The exenatide LAR has proved a significant improvement from the cardiometabolic point of view. The exenatide LAR has a security profile similar to that of the exenatide, and it is generally well tolerated.

All the glycemic and cardiovascular benefits when taking exenatide once a week are obtained without increasing the risk of hypoglycemia, without running the risk of putting on weight, and have a durability of effect of more than two years of treatment.

At present, we are looking forward to receive the results of the comparative studies between the two GLP-1 agonist receptors, i.e. exenatide LAR once a week and liraglutide once a day. The comparative data that we have at the moment are between the exenatide and the liraglutide. Both agonists are administered subcutaneous, the exenatide twice a day, the liraglutide once a day, and they have similar effects related to weight loss, while the average reduction of HbA1c under exenatide is between 0.5%-1% and the average reduction of HbA1c under liraglutide is 0.5%-1.6%. That is why, we hope that the latest underway comparative study in this field (DURATION-6) will clarify not only the quality of the metabolic balance but the cardiovascular efficiency as well.

Taspoglutide is a novel human GLP-1 analogue with minimal structural modifications, is administered as once weekly injection and improves overall glycemic control, produces clinically meaningful weight loss, well tolerated with minimal risk of hypoglycemia and no major safety concerns.

Taspoglutide benefits from the T-emerge study, a robust phase 3 program with global reach (T-emerge 1-8).

At present we know of two more 2 GLP-1 receptor agonists, but in studies of phase 2: Albiglutide and AVE 0010, which we are looking forward to receive.

The DPP-4 (dipeptidyl peptidase-4) enzyme have the role of inactivating the incretinic hormones after a period of 1-2 minutes, this being the average period of the incretinic effects. They can inactivate over 80% of the GLP-1 pool.

Consequently, DPP-4 inhibitors have the rol to prolong substantially the period of action of the incretinic hormones. The sitagliptine, the unique DPP-4 oral inhibitor to be found at present in the pharmaceutical network, approved in 2006, associated to diet and physical exercise, in combination to one or more oral antidiabetic agents, ameliorates the glycemic control in type 2 diabetes mellitus. The intake has to be reduced in case of moderate or severe renal insufficiency or of terminal renal insufficiency.

We can also find in investigational phase the vildagliptine, the alogliptine and the saxagliptine, belonging to the same family. They are either in FDA analysis or in phase 3 studies. All these four representatives are administered once a day orally, they are neutral or increase the weight curve and achieve the same average decrease of HbA1c (0.5%-0.8%). Nevertheless, there seems to be differences between them regarding the cardiovascular protection, aspect still in investigational phase.

The vildagliptine, marketed under the name of Galvus, has been approved for Europe but not for the United States, where the FDA has noticed a statistically significant association of the product with adverse cutaneous effects and increases of the hepatic enzymes. There have been complaints of headaches and nose-pharyngitis, while the hypoglycemic circumstances were under 1%.

The alogliptine is under FDA analysis and the saxagliptide in phase 3 studies. Lately, there have been discussions related to a new product named Ondero, but we do not have any other data about it.

Our experience, advanced in this field, shows that the incretines must not be used in the second therapeutic line exclusively, but that we should start administering them as soon as possible, when the function of a greater number of β-cells is intact [3].

Glucokinase inhibitors. The hexokinase family consists of the hexokinase 1, 2 and 3 (which have a molecular weight of 100 kDa) and the glucokinase, which has a molecular weight of 50 kDa. The glucokinase intervenes in the first phase of glucose metabolism and, thus, it has the function of catalyzing the transformation of glucose in the presence of the ATP in G6P (glucozo-6 phosphate) and ADP. The G6P inhibits the other hexokinases, but not the glucokinase which remains active in the β-cell and in liver.

At the level of the β-cell, the glucose, which enters with the help of the GLUT-2 transporter, under the catalytic action of the glucokinase, according to the above presented reaction, transforms itself into G-6-P and ADP, which will alter the intracellular ratio ADP/ATP , will close the K-dependent ATP channels, and will be followed by the depolarization of the cellular membrane and the opening of the calcium channels.

At the level of the liver, the G-6-P formation stimulates the glicolyse with the formation of glycogen, which will lead to a rate-limiting for glucose metabolism. Due to unknown reasons, in type 2 diabetes mellitus the activity of the glucokinase diminishes, and in type 2 diabetes mellitus with obesity the glucokinase diminishes its activity with 50% [4].

The glucokinase activators have as result an overexpression of hepatic glucokinase, with an increase of the glucose phosphorilation and of the glycogen synthesis. This therapy will lead to a decrease in hepatic glucose production, the increase of the Vmax for glucose phosphorilation, increased glucokinase binding affinity for glucose, increased glucose-dependent insulin secretion. Thus, the glucokinase activators will have a dual effect: 1.increased insulin secretion; 2.increased hepatic glucose uptake [4].

Glucagon antagonists. Due to unknown reasons, in type 2 diabetes mellitus, hepatic glycogen level is half that of non diabetes mellitus and, as a consequence, hepatic glucose production is 25% greater in diabetes mellitus than in non diabetes mellitus. So, because in the case of diabetes mellitus the glucogenesis is increased, a therapeutic solution would be to control the glucogenesis.

Of the researches currently developed on rodents we mention glucagon suppression by somatostatine, which will finally lead to increased glycogen synthesis, or glucagon antibodies, which have as a result decreased fasting glucose and glucose intolerance impairment.

Of the fundamental research in the field I would also like to mention the glucagon receptor antisense oligonucleotide or oral glucagon receptor antagonist (Bay 27-9955), which determines a 50% decrease of glucose level. In consequence, the blocking of the action of the glucagon could be a possible approach in the treatment of the diabetes.

Sirtuins. A great expectation in the treatment of type 2 diabetes mellitus are the sirtuins. The discovery belongs to David Sinclair from Harvard University, who consequently became the co-founder of the Sirtris company. The Sirtuins are considered at the moment very efficient medicines in the treatment of old age and of type 2 diabetes mellitus. Sirtuins are nicotinamide adenine dinucleotide-dependent histone acetylases, found in all living organisms and play general roles in the repression of gene transcription and mediates effects of caloric restriction. Caloric restriction decreases diseases of aging as type 2 diabetes mellitus, cancers, atherosclerosis, or cataracts, decreases glucose levels, decreases insulin levels, increases mythocondrial activity and number.

The Sirtuins contain activating compounds (STACs) of which the best known is the Resveratrol, found in red wine. The STACs bind N-terminus of SIR 1 leading to an allosteric activation. [4] SIR is an enzyme which in liver, skeletal muscle and white adipose tissue controlling fatty acid oxidation and gluconeogenesis, and in β-cell increases insulin secretion.

Resveratrol (SRT 501) by Sirtris is in phase 2 studies (SIRT 1 activation). It decreases blood glucose, increases insulin, extendes lifespan by 30%, attenuates cardiovascular diseases by decresing atherosclerosis and increasing aortic distensibility and decreases osteoporosis. They act by activating PPAR-γ co-activator (PGC-1) and increasing mythocondrial biogenesis.

Finally, we must mention Muraglitazar (PPAR α/γ activator), which increases SIRT-1. It has been withdrawn because of adverse cardiac effects [4].

SGLT2 inhibitors. They are inhibitors of renal sodium-glucose transporter-2. For many years, induction of glycosuria by a non-selective inhibitor of renal and intestinal glucose transport, named phlorizin, improves control of diabetes mellitus in animal models. This asked for the development of drugs that selectively target SGLT2 transporter with no side effects.

The renal reabsorption of the glucose takes place at the level of segments S1, S2 and S3 of the proximal renal tubules. The SGLT2 acts in segments S1 and S2, being responsible for the reabsorption of over 90% of the glucose, while the SGLT1 acts in segment S3, retaining only 10% of the reabsorbed glucose. That is why these inhibitors are created for the blocking of the T2 transporter [5].

Of this class we can mention so far the Sergliflozin and T1095, but which, out of various reasons, have not gone beyond phase 2. Our hope is for the Dapagliflozin (BMS 512148), which is a selective SGLT2 inhibitor with 1000-fold selectivity over SGLT1. In phase 2 study, doses of 5-10 mg/day increases urinary glucose excretion between 45-80 g/day and improves glucose tolerance.

Few patients complained polyuria, none nicturia, but in all patients it was a weight loss of 2.5-3.4 kg by energy deficit, not a compensatory increase in hunger and, simultaneously, an increased urinary sodium excretion, with a slight drop in systolic blood pressure.

Another one is the Remogliflozin Etabonate, novel SGLT2 inhibitor 60-fold selective over SGLT1. (5) The last agent is ISIS 388626, a novel approach to SGLT2 inhibition, using a RNAase H chimeric antisense oligonucleotide to "knockdown" expression of the SGLT2 gene in vivo. The drug reduces SGLT2 expression by up to 80% with once-weekly administration. It has a long duration of action, but still now only in rodent and dogs [6].

Of the fundamental researches I would like to mention 11β-HSD 1 inhibition which ameliorates metabolic syndrome and prevents progression of atherosclerosis in mice (7) or effects of an aldose reductase inhibitor or erythrocyte fructose 3-phosphate and sorbitol 3-phosphate levels in diabetic patients [8].

The future of the world diabetology is promising and we believe that the research in the field will soon lead to even more important results.

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