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Clinical study on the therapeutic efficacy of the dipeptidyl peptidase 4 inhibitors, in type 2 diabetes

PhD Thesis Abstract

Key words: diabetes type 2, DPP-4 inhibitors, sitagliptin, vildagliptin.

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CONTENTS

1. CURRENT STATE OF KNOWLEDGE ON INCRETIN THERAPY IN TYPE 2 DIABETES

1.1. Type 2 Diabetes mellitus - epidemiology and the need for new therapeutic options

The incidence and prevalence of type 2 diabetes mellitus (T2DM) greatly increases worldwide, especially in countries where lifestyle is sendentar and diet is high in calories and consists of cheap food. Growth is expected to double in prevalence over the next 20 years. It is estimated that 440 million people will be diagnosed with type 2 diabetes by 2030 (International Diabetes Federation 2009).[1] Moreover, the prevalence of type 2 diabetes changes increasingly affecting especially young groups of the population, with a high and increasing incidence in children and adolescents. [2]

The prevalence of diabetes varies significantly depending on the studied population, age, sex, socio - economic status and lifestyle. Predictions for 2025 are worrying and assessed by the American Diabetes Association, diabetes prevalence will reach 9%.

A large number of patients with type 2 diabetes treatment is not effective and does not meet therapeutic goals, mainly achieves almost abnormal glycosylated hemoglobin (HbA1c), representing a criterion for acceptable glycemic control. Important parameters such as weight loss and prevention of hypoglycaemia, are touched often. Insufficient metabolic control in type 2 diabetes is associated with the development of micro and macrovascular complications, increasing the risk of cardiovascular mortality and 75% of patients with type 2 diabetes die due to cardiovascular events. Risk of micro and macrovascular complications can be decreased by improving metabolic control.[3,4]

1.2 Incretins

Chronic hyperglycemia that characterizes type 2 diabetes results from the combination of two pathogenic mechanisms that influence each other: decreased insulin secretion and insulin resistance. In addition, due to damage pancreatic alpha cells, there is a high concentration of glucagon, which paradoxically increased after administration of glucose or after ingestion of carbohydrates. Unfortunately, none of the currently available classes of the antihyperglycemic agents do not act on all these components pathogens. For this reason there are a number of limitations to their effectiveness, evidenced by inadequate control of postprandial hyperglycemia, side effects such as weight gain, digestive intolerance or increased risk of hypoglycaemia.

Incretin-based therapies addressing multiple aspects of the patho- physiological mechanisms of the disease. GLP-1 receptor agonists mimic the effects of endogenous GLP-1, while DPP-4 inhibitors prevent rapid degradation of the hormone.

Both GLP-1 receptor agonists and DPP-4 inhibitors minimize the risk of hypoglycemia seen in insulin and some oral anti diabetic drugs. Treatment with GLP-1 receptor agonist or a DPP-4 inhibitor could produce an improvement in β-cell function in humans. This would be important because β-cell mass and β-cell function is already significantly lower for the moment in type 2 diabetes diagnosis , in general.

1.3 Glucagon-like peptide-1 action (GLP-1)

GLP-1 is cleaved post-translational pre proglucagon L neuro endocrine cells of the intestinal mucosa and the nervous system, but not in pancreatic alpha cells. Binds to GLP-1 receptors belonging to protein-coupled receptors G.[5] GLP-1 stimulates the secretion of pancreatic beta cells and also inhibits the alpha cell glucagon secretion. These two actions are strictly dependent on glucose production and lead to a normalization of glucose both fasting and postprandial. In terms of hypo glycaemia, counter-unaffected by glucagon and insulin secretion is stimulated. GLP-1 is therefore able not only to produce hypoglycemia.

1.4 Indications incretin-based therapies in the treatment guidelines for type 2 diabetes

DPP-4 inhibitors sitagliptin, vildagliptin and saxagliptin are approved in many countries for use in combined oral therapy when treatment goals are not achieved only through lifestyle changes and treatment with metformin. In this regard, DPP-4 inhibitors have a place in the German guidelines and a recommendation by the "British National Institute for Health and Clinical Excellence" (NICE) for patients should not be treated with sulfonylureas in order to avoid hypoglycaemia and weight gain.[6,7] A recent retrospective study showed that the incidence of hypoglycemia may promote the development of dementia.[8] As shown in NICE, avoiding hypoglycemia is an important target.

Data that has followed for 10 years UKPDS study show that early treatment of diabetes decreases significantly not only microvascular, but also the macrovascular complications. In relation to the results of this study, new diagnosed type 2 diabetes patients should have one treatment that achieves normoglycemic in a safe manner without the risk of hypoglycemia or weight gain.

Both incretin-based treatments were placed in initial or advanced stages of type 2 diabetes, when have been proved effective. Preliminary data showed that adding a DPP-4

inhibitor to existing insulin therapy lowers HbA1c and may have positive effects on hypoglycemic events.[9,10]

2. CONTRIBUTIONS

2.1. The main objective

Evaluate the efficacy of DPP-4 inhibitors as add-on therapy to OADs in reducing glycosylated hemoglobin in patients with insufficiently controlled type 2 diabetes.

Secondary objectives

1. The evaluation of the effectiveness of therapy with sitagliptin in reducing fasting glucose as add-on therapy to OADs for 12 months, administered in patients with type 2 poorly controlled diabetes.

2. The evaluation of the effectiveness of therapy with vildagliptin in reducing fasting glucose as add-on therapy to OADs for 12 months, administered in patients with type 2 diabetes poorly controlled.

3. The evaluation of DPP-4 inhibitors on lipid parameters (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides), on renal function (albuminuria, urea, creatinine, uric acid), on body weight, blood pressure and oscilometric index in patients with type 2 diabetes, treated for 12 months.

4. The identification , recording and evaluation of adverse reactions during treatment with DPP-4 inhibitors.

2.2 Material and methods

In the study were included 75 patients diagnosed with type 2 poorly controlled diabetes, treated with known antihyperglycemic, to which were added DPP-4 inhibitors, and were followed for 12 months after the beginning of incretin therapy, evaluate clinical and biologic at beginning of therapy, at 3 months, 6 months and 12 months. In the first month of treatment with DPP-4 inhibitors, 5 patients dropped out the study due to gastrointestinal side effects (diarrhea).

Clinical examination of patients included cardiology, ophthalmology, neurology and nephrology examination, determining anthropometric data (height, weight and body mass index), central hemodynamic parameters, frequency of cardiac contractions, systolic blood pressure, diastolic blood pressure.

Laboratory investigations included fasting plasma glucose, HbA1c, serum lipids, urea, creatinine, uric acid, ALT, AST, CBC, albuminuria.

2.3 Statistical processing methods

To determine the effect of treatment with DPP-4 inhibitors and the incidence of adverse reactions in patients included in the study was necessary a statistical analysis of details in order to accept or reject the null hypothesis: - TREATMENT HAS NO EFFECT - within a risk of 5% (0.05), a widely accepted risk in such studies.

Because the data did not meet the conditions for using the Student test (t) in order to compare the mean - in our case means and standard deviation were not equal for statistical samples compared, we applied Wilcoxon Signed Ranks test, an alternative to Student-t test used when the population distribution is not normal. Spearman correlation coefficient was used to analyze the relationship between data sets in our study.

2.4 RESULTS

2.4.1 Characteristics of carbohydrate metabolism parameters

All patients included in the study, regardless of antihyperglycemic therapy previously administered after the introduction of DPP-4 inhibitors (sitagliptin or vildagliptin), showed significant decreases in fasting plasma glucose and HbA1c.

After the first 3 months of treatment with DPP-4 inhibitors, fasting glucose (mg/dl) decreased from 148.27 ± 44.68 to 128.94 ± 22.71, and HbA1c (%) at 7.40 ± 1.39 to 6.93 ± 0.78. Values of the two parameters continued to decline until month 12 of follow-up, but to a lesser extent, so that the mean fasting glucose (mg/dl) was 127.58 ± 20.91 and HbA1c (%) was 6.72 ± 0.52.

2.4.2 Characteristics of lipid metabolism parameters

Regarding lipid metabolism, there was a slight decrease, but sustained a total cholesterol (mg/dl), so from 199.58 ± 42.06 at baseline, were values of 185, 58 ± 28.60, at month 12.

LDL-cholesterol (mg/dl) decreased slightly from 116.42 ± 31.51, at baseline to 104.30 ± 26.74, at the end of the study, after 12 months of therapy with DPP-4 inhibitors, respectively. Regarding HDL-cholesterol and triglycerides were not significant changes during the 12 months.

2.4.3 The safety profile of therapy with DPP-4 inhibitors

Therapy with DPP-4 inhibitors was well tolerated. We note that during the entire period of the study, there were no significant hypoglycaemia, even in patients treated with metformin + SU as first-line medication. This demonstrates that the administration of DPP-4 inhibitors as add-on therapy, not at risk of hypoglycemia.

Blood biochemistry (ALT, AST, creatinine, urea, uric acid) did not change significantly after 12 months of combination of a DPP-4 inhibitor to standard treatment of diabetes type 2. There was no case of acute pancreatitis.

2.4.4 Patients insulin treated

Insulin therapy in patients with type 2 diabetes is often initiated as OADs and is at least partly maintained. Therefore, it may be also possible to speculate on the clinical efficacy of the combination of a DPP-4 inhibitor with insulin.

All studies reported consistent results, with a mean reduction in HbA1c levels of 0.5 to 0.6% when insulin dosage remained unchanged.[11,12,13]

In our study, it is emphasized that the average age of patients who received insulin was 80 ± 5.50 years, as compared to 74.42 ± 7.63 years average age of the entire study group, the age of diabetes in these patients was 147.5 ± 30.11 months, compared with 78, 82 ± 46.31 months in the whole study group. Analyzing these values we found that both age and especially age diabetes patients were higher significantly in 8 patients who received insulin in period of the study compared with the entire study group ($p < 0.05$, $p < 0.0001$), which could explain the worse outcome of treatment with DPP-4 inhibitors in achieving optimal diabetes control and thus introducing insulin therapy.

3. CONCLUSIONS

1. Incretin hormones play an important role in maintaining glucose homeostasis and imbalance incretin system is a pathological feature of type 2 diabetes.

2. GLP-1 receptor agonists and DPP-4 inhibitors are two new pharmacological approaches to correct incretin system impairment in patients with type 2 diabetes.

3. Conventional treatments do not prevent development of type 2 diabetes due to decreased pancreatic beta cell function. Using DPP-4 inhibitors, patients with type 2 diabetes benefit from reductions in glucose levels, lower risk of hypoglycemia and potential long-term benefits, in terms of pancreatic beta-cell function and cardiovascular risk.

4. In our study, performed with sitagliptin and vildagliptin in combination with other oral antidiabetic therapy on a group of patients with type 2 diabetes, glycemic profile was significantly improved after 12 months of treatment, with a significant decrease towards normal values of HbA1c.

5. In our study, all 20 patients who had been managing, at baseline, triple therapy with oral antidiabetic agents without adequate control of diabetes, had an unique option that of introducing insulin therapy. After the administration of DPP-4 inhibitors (sitagliptin, vildagliptin), glucose metabolism in these patients was improved, so that only 8 patients

received insulin during the 12-month study, proving that incretin therapy may delay the time of introduction of insulin .

6. Cardioprotective effects of DPP-4 inhibitors are exercised through their action on quantitative growth incretin hormone GLP-1 and GIP, resulting in an increased sensitivity of the myocardium to insulin, myocardial glucose uptake and prevent cardiomyocyte apoptosis. In this study, we did not find any cardiocirculatory impaired, although the group was represented mostly by elderly patients.

7. Considered that there are several factors responsible for type 2 diabetes and its complications, one ideal treatment should provide durable glycemic control, maintain cell function, be neutral body weight, reduce the risk of cardiovascular disease and minimise the risk of hypoglycemia.

8. DPP-4 inhibitors therapy may be effective for reducing body weight only for patients with great weight, as our study showed, for a BMI between 35 to 39.9.

9. In this study, DPP-4 inhibitors (sitagliptin and vildagliptin) as add-on therapy to metformin, sulphonylureas, or glitazones, did not alter systolic or diastolic blood pressure.

10. The study showed that the average of total cholesterol decreased significantly during the first 6 months, then slowly decreased throughout the period of the study, which demonstrates that sitagliptin and vildagliptin improves total cholesterol in patients with type 2 diabetes.

11. Significant difference between mean values albuminuria, registered in assessing the month 12 and month 3, and between month 12 and month 6 shows that DPP-4 inhibitors, administered over a period of time (over 6 months), improved the microalbuminuria, which leads to a reduction of ischemic cardiovascular risk in patients with type 2 diabetes.

12. The appearance of the mild nonproliferative diabetic retinopathy, highlighted in 37 patients of the 70 patients included in the study, did not become over time, observing the appearance of even a slight improvement in 4 patients, proving that therapy with inhibitors DPP-4 can delay the onset of diabetic retinopathy.

13. In our study, sitagliptin administered at a dose of 100 mg once daily and vildagliptin 50 mg administered twice daily for 12 months did not produce significant side effects, although patient age was investigated 74.4 ± 7.6 years.

14. The safety profile of DPP-4 inhibitors used in the study (sitagliptin and vildagliptin) was good, hepatic and renal functions, blood counts were slightly changed after 12 months of treatment in combination therapy with other oral antidiabetic agents.

15. Side effects were only present in the gastrointestinal area (diarrhea) - five patients (2 treated with sitagliptin and vildagliptin 3) abandoned the study during the first month of therapy.

16. The incidence of hypoglycaemia was similar before and after treatment with sitagliptin or vildagliptin, which proves that DPP-4 inhibitors not presented hypoglycemia risk.

17. This group of new drugs is another step in the progress toward personalized medicine and specifically prescription of the incretins therapy to patients, based on personal criteria.

18. Potential disadvantages of DPP-4 inhibitors include cost and relative lack of information on the efficacy and safety of long-term.

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