SCHOLASTIC:
Journal of Natural and Medical Education
Volume 2, Issue 6, Year 2023 ISSN: 2835-303X
https://univerpubl.com/index.php/scholastic

Trelagliptin in the Treatment of Patients with Type 2 Diabetes Mellitus - Efficacy and Safety

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Article Information

Received: April 25, 2023
Accepted: May 23, 2023
Published: June 24, 2023

Keywords
type 2 diabetes mellitus; dipeptidyl peptidase-4 inhibitors; safety; trelagliptin; vildagliptin.

ABSTRACT

This article discusses the efficacy and safety of Vedic 100 mg (trelagliptin) in patients with type 2 diabetes mellitus (DM). The drug belongs to the group of DPP-4 inhibitors, to be taken once a week. This drug controls blood glucose levels by selectively and permanently inhibiting DPP-4, an enzyme that causes the inactivation of glucagon-like peptide-1 and glucagon-dependent insulinotropic polypeptide, incretin hormones that play an important role in the regulation of blood glucose levels. The drug was taken in combination with metformin for a month. The drug was prescribed to patients (n-24) with type 2 diabetes, with a glycated hemoglobin of 7-9%, who were on metformin monotherapy before the study. Trelagliptin 100 mg was added to metformin once a week. The results showed that the drug has a positive effect on the main metabolic disorders of DM and allows achieving compensation of

carbohydrate metabolism, as indicated by a decrease in fasting glycemia by 20% ($p<0.05$), postprandial glycemia by 18% and glycated hemoglobin by 16%. Improvements in lipid metabolism were also noted. However, none of the patients experienced hypoglycemia.

INTRODUCTION

Type 2 diabetes mellitus (DM2) is a major medical problem in most countries of the world. Traditional hypoglycemic drugs are not able to provide long-term glycemic control and affect the natural course of T2DM [1].

The prevalence of diabetes mellitus (DM) in the world is steadily increasing every year. According to the International Diabetes Federation (IDF), in 2021, about 537 million people had this disease, and according to forecasts, by 2045, this patient population is expected to increase to 783 million people [5]. Type 2 diabetes mellitus (DM2) is a chronic progressive disease that includes a complex of pathophysiological disorders [2]. Despite the fact that almost all oral antidiabetic drugs (OSBPs) are generally effective in lowering blood glucose levels, none of them is able to maintain adequate glycemic control over a long period of time [2]. Metformin, which is one of the most common and widely used first-line drugs worldwide in the treatment of T2DM, does not achieve glycemic goals in a significant proportion of patients [3,4]. Thus, long-term disease management requires intensification of therapy after a certain period of time [3]. Achieving long-term goals of glycemic control is associated with the need to foresee potential side effects of therapy in order to provide an optimal balance between good disease control and minimal risk of adverse events that affect the prognosis of the disease and quality of life in patients with type 2 diabetes [3,6]. Due to the wide prevalence of DM2 and the inevitable need for combination therapy in such patients, it is extremely important to evaluate various regimens of hypoglycemic therapy in real clinical practice. The questions of the choice of drugs in terms of safety for the correction of glycemia in type 2 diabetes in combination with coronary artery disease remain relevant. In this regard, a new class of hypoglycemic drugs based on the incretin effect, which include dipeptidyl peptidase 4 (DPP-4) inhibitors, is of interest [3,4,10]. The role of DPP-4 inhibitors with a fundamentally new mechanism of action is becoming increasingly important and opens up new opportunities for restoring the physiological function of alpha and beta cells of the pancreatic islets in type 2 diabetes, making it possible to slow down the progression of the disease.

When DPP-4 is inhibited, the activity of incretins is prolonged, which, in turn, increases the level of active incretins in the blood circulation. As a result, the imbalance of the insulin / glucagon ratio is normalized: glucose-dependent insulin secretion by β-cells increases, and glucagon secretion by α-cells is suppressed, which allows you to effectively control glycemic control against the background of a significant reduction in the risk of hypoglycemia, especially severe episodes, due to glucose-sensitive action [10,12 ,13]. Improved islet cell function leads to improved glycemic control. The ideal hypoglycemic drug should be effective, safe, convenient to use, able to prevent the progressive deterioration of pancreatic β-cell function during long-term treatment, and positively influence the outcomes of diabetes. The use of the effect of incretins in

the last decade is a new and promising direction in the treatment of type 2 diabetes. The questions of the choice of drugs in terms of safety for the correction of glycemia in type 2 diabetes in combination with coronary artery disease remain relevant. In this regard, a new class of hypoglycemic drugs based on the incretin effect, which include dipeptidyl peptidase 4 (DPP-4) inhibitors, is of interest [6,11,12]. The role of DPP-4 inhibitors with a fundamentally new mechanism of action is becoming increasingly important and opens up new opportunities for restoring the physiological function of alpha and beta cells of the pancreatic islets in type 2 diabetes, making it possible to slow down the progression of the disease. Trelagliptin (Vedika) is a once-weekly dipeptidyl peptidase-IV (DPP-4) inhibitor. This drug controls blood glucose levels by selectively and permanently inhibiting DPP-4, an enzyme that causes the inactivation of glucagon-like peptide-1 and glucagon-dependent insulinotropic polypeptide, incretin hormones that play an important role in the regulation of blood glucose levels. Inhibition of DPP-4 increases insulin secretion in a manner dependent on blood glucose concentration, thereby controlling blood glucose levels. Vedic is available in the form of tablets for oral administration at a dose of 100 mg [7,8]. It is necessary to discuss the possibilities of modern innovative incretin drugs that complement the clinician's therapeutic arsenal by improving the function of b-cells, enhancing glucose-dependent insulin secretion with a low risk of hypoglycemia, suppressing increased secretion of glucagon, favorable cardiovascular effects, and the ability to control body weight. Perhaps this rapidly developing area of diabetes therapy will make it possible to get closer to solving the problem of the effectiveness and safety of glycemic control in a vulnerable category of patients with type 2 diabetes.

Purpose of the study.

To determine the efficacy and safety of the dipeptidyl peptidase-4 (DPP-4) inhibitor Vedic (trilagliptin) in therapy in patients with type 2 diabetes mellitus (DM).

MATERIALS AND RESEARCH METHODS.

The clinical study was conducted on the basis of the TMA multidisciplinary clinic, in the department of 2-therapy and endocrinology. In 50 patients with type 2 diabetes, the initial and after treatment levels were determined: fasting and postprandial glycemia, glycated hemoglobin (HbAlc), blood lipid profile. Patients with type 2 diabetes had cardiovascular diseases such as hypertension 70% and coronary heart disease 45%. The duration of DM disease ranged from 3 to 8 years, the average age of the surveyed was 56.6±9.8 years, among them 31 women and 19 men. From instrumental studies, ECG, EchoCG, and blood pressure studies were carried out. Blood glucose was studied by biochemical method (SPINREACT kits, S.A.U.). The study of glycated hemoglobin (HbA1c) was carried out according to the biochemistry method (FILTERSAMPLER kits).

Lipids (TC, TG, LDL-C, HDL-C) were determined by biochemical method (SPINREACT kits, S.A.U.). The data obtained are presented as a percentage or as an average error (M±m). Statistical data processing was carried out using the STATISTICA software system for Windows (version 9.0). To clarify the relationship between the studied indicators, a correlation analysis was carried out with the calculation of the Pearson correlation coefficient. The criterion of statistical significance of the results obtained was the value of $p<0.05$.

RESULTS OF THE STUDY

Vedika (trelagliptin) was used as a drug from the class of dipeptidyl peptidase-4 inhibitors. Trelagliptin is a new long-acting dipeptidyl peptidase-4 (DPP-4) inhibitor that is taken once a week [4,8]. The study included patients who before the study were on monotherapy with metformin (M) at a dose of 500 mg to 1500 mg per day. Randomized patients with HbA1c from at least 7% to less than 9% were divided into 2 groups: group 1 patients (n-24) took trelagliptin 100 mg once a week, group 2 - vildagliptin 50 mg (n-26) twice per day along with metformin for a month. The control group consisted of 20 adults without DM, 5 (25%) of them had AH, comparable in age, 55.9±7.5 years.

Table 1

Clinical characteristics of patients depending on randomization

Characteristics of the examined patients	Control	Control	Control
Index	8 (40%)	12(50%)	7(26,9%)
Men	12(60%)	12(50%)	19 (73,1%)
Women	55,9±7,5	55,9±3,8	56,5±7,1
Age, years	29,5±6,4	33,4 ±8,1	34,4 ±5,9
Body mass index, kg/m2	5 (25%)	13 (54%)	20 (76,9%)
Duration of history of DM 2, years	-	5,5 (3,0; 8,0)	4,5 (3,5; 8,0)
SBP, mm Hg	133,5±11,3	157,2±13,5	157,7±14,3
DBP, mm Hg	88,7±5,8	98,1±7,4	98,34±7,6
Heart rate, bpm	76,0±9,1	77,11±8,89	78,28±9,07
LVH, %	59,7%	83,7%	89,5%
Angina FC I-II	-	4 (9,5%)	8 (19,0%)

As the data in Table 1 show, the examined patients have 1 degree obesity, 83.7% and 89.5% of the examined patients have left ventricular hypertrophy (LVH). LVH is regarded as the main predictor of cardiovascular mortality.

Analysis of carbohydrate metabolism data showed that all patients had unsatisfactory values of carbohydrate metabolism at admission. So, in 2 examined groups, there was an increase in carbohydrate metabolism compared to the control group, while fasting glycemia was increased by 52% and 54%, postprandial by 48% and 43% and HbA1c by 37% and 39%, respectively. . It should be noted that all these patients were on metformin monotherapy prior to inclusion in the study. Also, patients had dyslipidemia with an increase in TC, triglycerides, LDL and a decrease in HDL. It is known that poor glycemic control and dyslipidemia are important risk factors for the development of cardiovascular diseases in patients with type 2 diabetes [6,11].

Table 2.

Biochemical parameters of blood in patients with type 2 diabetes before and during treatment

Indicators Control	Indicators	Indicators	Indicat	Indicators Control	Indicator

	Control	Control	ors Control		s Control
Fasting glycemia, mmol/l					
Initially	4,5±1,0	8,5±1,0	0,039	8,7±1,7	0,031
After 12 weeks		6,9±1,9		6,7±1,6	
Postprandial glycemia, mmol/l					
Initially	6,3±1,3	14,5±3,0	>0.05	13,9±1,0	0,044
After 12 weeks		9,9±1,9		9,0±2,1	
HbA1c, %					
Initially	5,5±0,9	8,8±1,0	>0.05	8,8±1,3	>0.05
After 12 weeks		7,4±1,6		7,1±1,2	
Total cholesterol, mmol/l					
Initially	4,3±0,7	5,1±1,7	>0.05	4,8±1,4	>0.05
After 12 weeks		4,5±1,9		4,6±1,7	
Triglycerides, mmol/l					
Initially	1,5±0,08	2,46±1,51	0.028	2,51±1,82	0.014
After 12 weeks		1,95±1,23		1,82±1,55	
HDL, mmol/l					
Initially	1,35±0,4	0,92±0,33	>0.05	0,96±0,37	>0.05
After 12 weeks		0,98±0,31		1,01±0,40	
LDL, mmol/l					
Initially		2,12±1,8	>0.05	2,55±1,30	>0.05
After 12 weeks		2,03±2,16		2,18±1,84	
AST, U/l					
Initially	17,9±3,9	31,6±7,2	>0.05	33,1±6,8	>0.05
After 12 weeks		22,6±8,4		21,4±7,0	
ALT, U/l					
Initially	21,8±3,4	37,5±9,6	>0.05	39,8±10,1	>0.05
After 12 weeks		31,3±9,1		32,1±8,8	

Note: $p<0.05$ – the presence is significant in relation to the studied group

In group 1 patients, trilagliptin at a dose of 100 mg/week was added to metformin. The 2nd group of patients took the drug Vildagliptin at a dose of 100 mg per day. The dose of metformin was increased to 2000 mg/day.Against the background of treatment, there are positive dynamics in carbohydrate metabolism. So, in patients of group 1, fasting glycemia was reduced by 20% ($p<0.05$), in group 2 - by 21% ($p<0.05$), postprandial glycemia by 18 ($p>0.05$) and 33% ($p<0.05$), there is a positive trend, while HbA1c in the groups was reduced by 16 and 17.5% ($p>0.05$), respectively. About half of patients with type 2 diabetes could not achieve the target HbA1c while taking trelagliptin and vildagliptin for a month. During treatment, in patients with DM, lipid metabolism indicators significantly changed in a positive direction in both groups, which may be associated with the elimination of glucose toxicity and an increase in tissue

sensitivity to insulin, which largely determine the rate of formation and metabolism of lipids in the body [3].

So, TC in both groups was reduced by 12 and 9% (p>0.05), respectively. The content of liver enzymes in patients of both groups did not change.

It should be noted that all patients who took Trelagliptin 100 mg once a week noted the convenience of taking this drug, in comparison with patients who took Vildagliptin 50 mg daily, twice a day.]. Effective therapy for type 2 diabetes is associated with weight gain. Weight gain, for example, is the most common side effect According to the literature, Trelagliptin is well tolerated both alone and in combination with other antidiabetic drugs [7]. The advantage of trelagliptin over existing once-daily DPP-4 inhibitors is to reduce the frequency of taking the drug once a week [7 the effect of insulin therapy, taking traditional PSSP. This is fraught with aggravation of insulin resistance, deterioration of the clinical picture of the disease, and an increase in the cost of treatment. So, for 4 weeks of observation in patients of groups 1 and 2, there was no increase in body weight. Thus, the results of this study largely coincide with the conclusions of foreign authors [7]. Also, in patients of group 1, there was a decrease in systolic blood pressure from 157.7±14.3 mm Hg. up to 139±9.7 mm Hg. Art. (p<0.05), diastolic with 98.34±7.6 mm Hg. up to 85.7±4.4 mm Hg (p<0.05). Similar changes were observed in patients of group 2, because All patients received antihypertensive therapy.

Analyzing the side effects, it should be noted that patients of groups 1 and 2 did not experience hypoglycemia. In addition, no specific serious adverse events have been reported by patients, making it an attractive alternative to other DPP-4 inhibitors. Thus, the long-acting drug Trelagliptin (Vedika) is as highly effective and safe as Vildagliptin. The drug ensures the achievement of glycemic control goals without complications and side effects. One of the main advantages of this drug is the possibility of use in people with arterial hypertension, moderate renal impairment, as well as in patients at cardiovascular riskSince trelagliptin only needs to be taken once a week, this new drug may improve adherence and therefore glycemic control in patients with type 2 diabetes. The advantage of trelagliptin over existing once-daily DPP-4 inhibitors is the reduced frequency of dosing compared to once-a-week dosing.

Large-scale, long-term studies in the future will help further confirm its long-term efficacy and safety, patient satisfaction, and adherence to treatment.

The clinical study was conducted on the basis of the TMA multidisciplinary clinic, in the department of 2-therapy and endocrinology. In 50 patients with type 2 diabetes, the initial and after treatment levels were determined: fasting and postprandial glycemia, glycated hemoglobin (HbAlc), blood lipid profile. Patients with type 2 diabetes had cardiovascular diseases such as hypertension 70% and coronary heart disease 45%. The duration of DM disease ranged from 3 to 8 years, the average age of the surveyed was 56.6±9.8 years, among them 31 women and 19 men. Randomized patients with HbA1c from at least 7% to less than 9% were divided into 2 groups: group 1 patients (n-24) took trelagliptin 100 mg once a week, group 2 - vildagliptin 50 mg (n-26) twice per day along with metformin for a month. The control group consisted of 20 adults without DM, 5 (25%) of them had AH, comparable in age, 55.9±7.5 years. The results showed that the drug has a positive effect on the main metabolic disorders of DM and allows achieving compensation of carbohydrate metabolism, as indicated by a decrease in fasting glycemia by 20% (p<0.05), postprandial glycemia by 18% and glycated hemoglobin by 16%. Improvements in lipid metabolism were also noted. However, none of the patients experienced hypoglycemia.

Conclusions.

1. Combined hypoglycemic therapy with Trelagliptin and Metformin for a month has a positive effect on the main metabolic disorders of DM and allows to achieve compensation of carbohydrate metabolism, as indicated by a decrease in fasting glycemia by 20% ($p<0.05$), postprandial glycemia by 18% and glycated hemoglobin by 16%, compared with the control group, where all indicators were reduced, in particular, postprandial glycemia was significantly reduced by 33% ($p<0.05$). Also, this combination has a positive effect on lipid metabolism.

2. As a representative of DPP-4 inhibitors for the treatment of type 2 diabetes, Trelagliptin 100 mg per week. effectively and safely improved control in patients with diabetes and cardiovascular pathologies, while none of the patients experienced hypoglycemia.

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