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Pharmacotherapy of IDPP 4: benefits of modern diabetes management

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Annotation: The place of traditional sulfonylurea (SM) drugs that stimulate insulin secretion began to be occupied by incretin drugs , primarily dipeptidyl peptidase-4 (iDPP-4) inhibitors, due to their unique physiological glucose-dependent effect on the secretion of insulin and glucagon, allowing effective control of diabetes mellitus (DM) .) 2 types without significant side effects. Drugs of the DPP-4 class are recommended for use at all stages of the development of diabetes, starting from the onset, both in monotherapy and in combination with oral hypoglycemic drugs (PSP) and insulin. Cardiovascular safety, the ability to take in the late stages of chronic kidney disease (CKD), a neutral effect on body weight, ease of use are their undeniable advantages. The combination of iDPP-4 (for example, vildagliptin) with metformin is the most popular, covers the vast majority of pathophysiological defects in type 2 diabetes, is available in a fixed form (for example, Galvus Met). More than 10 years of experience in clinical practice with drugs of the DPP-4 class (for example, Galvus) suggests that their main clinical effects have been finally identified, they can be systematized and the established advantages and disadvantages in the management of type 2 diabetes can be discussed.

Abstract: Traditional medications of sulfonylurea (SU), which stimulate insulin secretion, have been edged out by incretin drugs, primarily dipeptidyl peptidase-4 (iDPP -4) inhibitors, due to their unique physiological glucose-dependent effect on insulin and glucagon secretion, allowing for effective control of type 2 diabetes mellitus (DM) without significant side effects. Drugs of iDPP-4 class are recommended for use at all stages of DM development, starting from the onset, both in monotherapy and in combination with oral antidiabetic drugs (OAD) and insulin. Cardiovascular safety, the possibility of admission at the tardive stages of chronic kidney disease (CKD), a neutral effect on body weight, ease of application are indisputable benefits. The combination of iDPP-4 (for example, vildagliptin) with metformin is the most popular, covers the vast majority of pathophysiological defects in type 2 DM, is available in a fixed form (for example, Galvus Met ®). The admission of drugs of the iDPP-4 class in clinical practice for more than 10 years (eg, Galvus ®) allows to consider that their main clinical effects are finally identified, they can be systematized and the established benefits and disadvantages in managing of type 2DM can be discussed.

Key words: diabetes mellitus, incretins , iDPP-4 , vildagliptin , metformin

Introduction

As defined by experts from the World Health Organization, "diabetes is a problem of all ages and all countries."

It is the only chronic non-communicable disease whose pandemic growth rates led to the adoption in December 2006 of a United Nations (UN) resolution calling for the establishment of national programs for the prevention, treatment and prevention of diabetes mellitus (DM) and its complications.

Findings from UK Prospective Large -Scale Research diabetes Study (UKPDS) and Diabetes control and Complications trial Research Group (DCCT) have convincingly demonstrated the importance of intensive glycemic control in the management of DM [1, 2, 3].

In recent years, considerable attention has been paid to the study of the role of two hormones of the gastrointestinal tract, which are actively involved in the regulation of insulin secretion, and, consequently, in the regulation of glucose homeostasis in the human body. These include glucagon -like pepti d- (GLP-1) and

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glucose-dependent insulinotropic polypeptide (GIP). One of the approaches to use the therapeutic effects of GLP-1 and GIP is the inhibition of the enzyme dipeptidyl peptidase-4 (DPP-4), under the influence of which they are rapidly deactivated in the body. The use of DPP-4 inhibitors, against the background of which an increase in the level of incretins is achieved , is a physiological way to restore impaired insulin production and correct glucagon levels - key disorders that are characteristic of DM2 .

The pathogenetically determined mechanism of action of this group of drugs allows them to be successfully used in most patients with DM 2 both in monotherapy and in combination with metformin and sulfonylurea drugs . In addition, we are now receiving increasing evidence that the use of DPP-4 inhibitors, such as vildagliptin , is effective even in the late stages of T2DM therapy [4, 5].

Studies have demonstrated high hypoglycemic efficacy of vildagliptin in patients with a relatively long course of the disease [6].

DPP-4 inhibitors significantly reduce basal and postprandial secretion of glucagon by pancreatic -cells, which can significantly improve glycemic control by reducing hepatic glucose production. Probably, it is due to the effect on glucagon secretion that the hypoglycemic effect of DPP-4 inhibitors is explained, including in patients with relatively low insulin secretion. At the same time, vildagliptin provides glucose-dependent regulation of the function of beta and alpha cells , so that the risk of hypoglycemia is minimal. Among the advantages of gliptins , one should also note their neutral effect on body weight dynamics and the possibility of their use in patients with reduced renal function.

Thus, it is of great interest to study the additional benefits that this group of drugs can provide in patients with long-term diabetes who have not achieved adequate control on insulin therapy. UKPDS data clearly demonstrated the steadily progressive nature of the disease [1].

Accordingly, the question of prescribing insulin eventually arises before the majority of patients with type 2 diabetes. The decision to start insulin therapy in patients with type 2 diabetes is often delayed. Hypoglycemic conditions, weight gain, the complexity of insulin therapy are the main limiting factors for timely intensification of therapy and the achievement of adequate control in a larger number of patients with type 2 diabetes on insulin therapy. Increased cardiovascular and overall mortality associated with severe hypoglycemia is considered in modern diabetology as one of the key problems, the solution of which is devoted to many efforts. In this regard, it is difficult to overestimate the value of drugs that, when added to insulin therapy, can improve glycemic parameters and at the same time do not increase the risk of hypoglycemic episodes. In this review, we will take a closer look at several studies demonstrating the beneficial effects of adding vildagliptin to patients on insulin.

The first trial of combination therapy with insulin and vildagliptin was completed in 2007 by V. Fonseca et al . [7]. This was a 24-week, multicenter, double-blind , placebo-controlled study in which patients with type 2 diabetes and inadequate glycemic control on >30 U / day NPH insulin (baseline HbA1c 7.5–11%) were added to either vildagliptin (n =144) at a dosage of 50 mg 2 times, or placebo (n=152). The duration of diabetes in those included in the study averaged 15 years.

In addition, all patients were on insulin therapy for more than 6 years. For 12 weeks, the regimen of insulin therapy in patients did not change. The mean daily dose of insulin was the same in both treatment groups (81 U in the insulin + vildagliptin group and 82 U in the insulin + placebo group).

After 24 weeks of observation, the HbA1c levels in the main group decreased by 0.5%, in the control group (insulin in combination with placebo) - by only 0.2%.

It is interesting to note that in patients aged 65 years and older, the combination of insulin with vildagliptin contributed to a decrease in the level of glycohemoglobin (HbA1c) by 0.7%, while in the control group there was no statistically significant difference in HbA1c dynamics depending on age [7] (Fig. 1).

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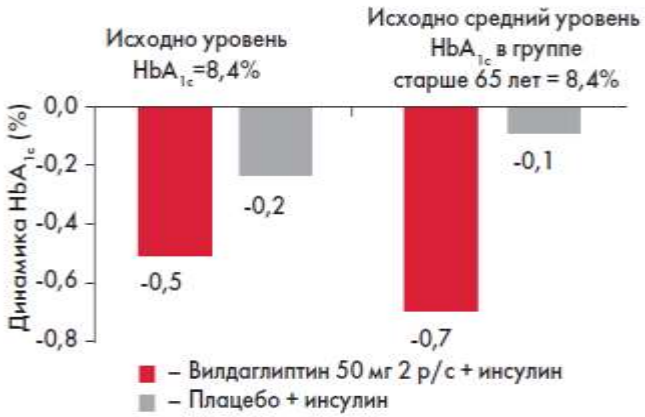

Рис. 1. Динамика HbA_{1c} в основной группе и группе пациентов старше 65 лет при добавлении вилдаглиптина к инсулину [7].

It should be noted that episodes of hypoglycemia were recorded much less frequently in the main group, which is probably due to an increase in the sensitivity of pancreatic α -cells to glucose, so in the placebo group 10 episodes of severe hypoglycemia were recorded, while in the vildagliptin group - 0 [7]. These data are extremely relevant, given both the progressive increase in the prevalence of type 2 diabetes in the older age group, and the increase in life expectancy of patients with a relatively early onset of the disease and, accordingly, the need to prescribe insulin therapy over time. It should also be emphasized separately that the risk of developing severe hypoglycemia in elderly patients is much higher [8]. In the 28-week extension of the main study, the dynamics of the decrease in the frequency of hypoglycemia in patients treated with vildagliptin + insulin became even more evident [9] (Fig. 2).

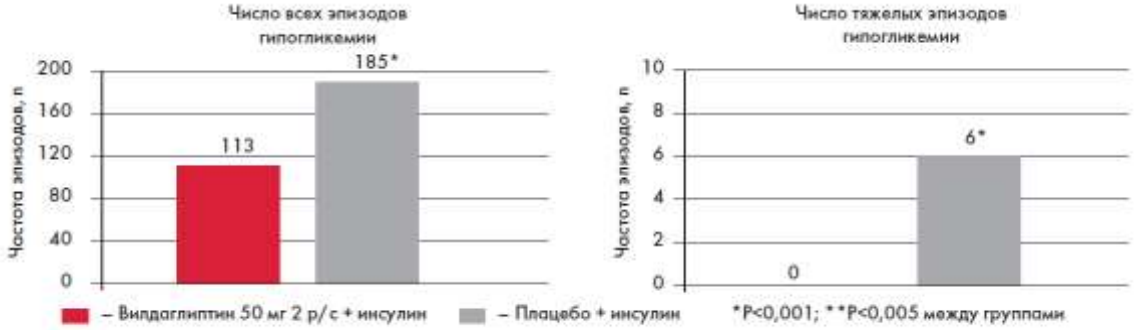

Рис. 2. Снижение риска гипогликемий при добавлении вилдаглиптина к инсулину [9].

PID-4 proved to be the first pharmacotherapeutic group to prove its cardiovascular safety in accordance with the new requirements of the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) [10,11].

The cardiovascular safety of vildagliptin was confirmed in a meta-analysis of adverse events from the cardiovascular (CV) system in 40 phase III and IV studies (more than 17 thousand patients) with an independent prospective peer review [12, 13]. The MHRR (Mantel - Haenszel hazard ratio) for major adverse CV event (MACE) for treatment with vildagliptin and comparators was 0.82 (95% CI 0.61–1.11). Similar hazard ratios (HRs) were determined for individual components of MACE such as non-fatal myocardial infarction (MI) (0.87, 95% CI 0.56–1.38), non-fatal stroke (0.84, 95% CI 0, 47–1.50) and death due to CVD (0.77, 95% CI 0.45–1.131) [13] (Fig. 3).

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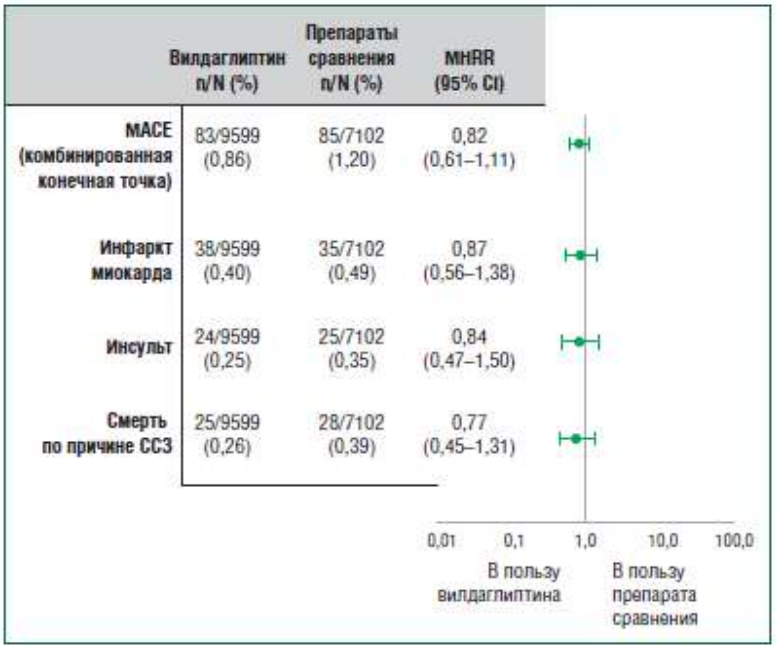

Fig.3
The incidence and OR of the combined endpoint MACE , its individual components while taking vildagliptin and comparators.

The placebo-controlled study TECO S (more than 14 thousand patients) on the cardiovascular safety of sitagliptin in patients with type 2 diabetes and CVD revealed a neutral effect of the drug on the achievement of the combined MACE endpoint in patients with high cardiovascular risk (11.4% in the sitagliptin group (100 mg/ day), 11.6% in the placebo group). In addition, both groups had a comparable rate of hospitalization for heart failure (HF): RR = 1.00 (CI 0.83–1.20); p =0.983. Sitagliptin or placebo were added to an existing SST (PSSP ± insulin therapy for at least 3 months) [14].

Similar results were obtained in a prospective placebo-controlled study of the SS safety of saxagliptin - SAVOR - TIMI (more than 16 thousand patients with type 2 diabetes with a history of a SS event or at a high risk of its development). Patients were randomized 1:1 to saxagliptin or placebo in addition to standard therapy. According to the results of the study, the saxagliptin group had no differences in both the primary MACE and the secondary endpoint — MACE+ (additional hospitalizations for unstable angina, coronary revascularization). However, in the saxagliptin group, there was a significant increase of 27% in the frequency of hospitalizations for CHF (3.5% in the saxagliptin group , 2.8% in the placebo group, p = 0.007; RR = 1.27; 95% CI 1, 07–1.51) compared with the control group, although without an increase in mortality [15].

The placebo-controlled VIVIDD study (254 patients with type 2 diabetes, randomized 1:1 to active treatment and placebo in addition to standard therapy for type 2 diabetes) on the safety of vildagliptin in patients with heart failure and reduced ejection fraction showed no significant differences with the control group in terms of the frequency of hospitalizations due to CHF (10.2% in the vildagliptin group , 8.0% in the placebo group, p = 0.552). These results seem to indicate a neutral effect of vildagliptin on the development or progression of CHF in patients with type 2 diabetes. Randomization in a 1:1 ratio to alogliptin and placebo treatment groups, about 28% of patients in both groups had CHF) also found no statistically significant effects of the drug in relation to events associated with CHF. However, in the alogliptin group, hospitalization for CHF was the first study event in 85 patients (3.1%) versus 79 (2.9%) patients in the placebo group (RR 1.07; 95% CI 0.79–1, 46). The absence of statistical significance of this difference does not exclude a possible vector towards an increase in the incidence of CHF with the use of alogliptin. The results of the conducted RCTs generally convincingly showed that this class of drugs should be considered as drugs with a neutral effect on the main cardiovascular endpoints (MACE and MACE +), i.e. they are quite safe in patients with type 2 diabetes with a high cardiovascular risk.

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The safety and efficacy of DPP-4i have also been proven in special groups of patients - elderly patients, who are characterized by concomitant multiple organ pathology and impaired recognition of hypoglycemia. The INTERVAL placebo-controlled trial in patients over 70 years of age from various European countries (24-week follow-up, vildagliptin was administered either as monotherapy or as adjunctive therapy with an individually adjusted glycemic target) convincingly demonstrated the possibility of achieving individualized HbA1c goals as an endpoint. points in this group of patients. The adjusted odds ratio for achieving the individually adjusted glycemic target was 3.16 (96.2% CI 1.81–5.52; $p < 0.0001$) in favor of vildagliptin without any tolerability and safety concerns [19, 20].

Conclusion

Summing up, we can say with full confidence that today iDPP-4 represent one of the most promising pharmacotherapeutic groups of PSSP. With their appearance in clinical practice, the treatment of type 2 diabetes has become more pathophysiologically substantiated, safe, and effective. The colossal evidence base for the efficacy and safety of this group of drugs has been demonstrated by the results of numerous RCTs, as well as studies in the RCP. The high safety of DPP-4 iDs in relation to cardiovascular risk, hypoglycemia, the possibility of their use in patients at any stage of CKD, patients of older age groups, as well as their neutral effect on body weight make them the most attractive for the treatment of patients with type 2 diabetes.

The combination of iDPP-4 (for example, vildagliptin) with metformin is the most popular, covers the vast majority of pathophysiological defects in type 2 diabetes, is available in a fixed form (for example, Galvus Met ®). The use of drugs of the DPP-4 class in clinical practice for more than 10 years (for example, Galvus ®) allows us to consider that their main clinical effects have been finally identified, they can be systematized and the established advantages and disadvantages in the management of type 2 diabetes can be discussed.

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