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PHARMACOECONOMIC EVALUATION OF SITAGLIPTIN COMPARED TO SULFONYLRUEA DERIVATIVES IN PATIENTS WITH TYPE 2 DIABETES NOT CONTROLLED BY METFORMIN MONOTHERAPY

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Summary:

Study objective: To perform a comparative pharmacoeconomic analysis of the therapy combinations: sitagliptin with metformin, and sulfonylureas with metformin in patients with type 2 diabetes on metformin monotherapy whose target glycemic goal is not reached with diet and exercise.

Materials and methods: A time horizon of 10 years was used to conduct the comparative pharmacoeconomic analysis. The following were used as reference data for the calculations: drug prices, as registered in the VED [Vital Essential Drugs]; earlier publications on the cost of complications; and data on treatment outcomes and hypoglycaemia rates in comparator groups from the JADE modelling study, based upon the data from clinical study 024 for the Russian patient population.

Results: Total medical expenditures for one patient came to 449,927 rubles in the sitagliptin+metformin group, and 415,385 rubles in the sulfonylurea+metformin group – a difference of 7.7%. Within this, the share of costs for the actual drugs was 53% and 11%, respectively, indicating a greater burden due to long-term consequences (hypoglycaemia, complications from type 2 diabetes, transitioning to insulin) for the sulfonylurea group. When converted to 10,000 patients, the cost of the drugs in the sitagliptin group was 2,149 million rubles higher, and the expenditures for complications, including hypoglycaemia and insulin therapy, were 1,559 million rubles lower. Thus, in the sitagliptin group – unlike the sulfonylurea group – 410,000 cases of hypoglycaemia were prevented, as well as 40 cases of macro- and micro-vascular complications.

Conclusion: the results suggest that the combination use of sitagliptin + metformin is pharmacoeconomically justified when compared to sulfonylurea + metformin to treat type 2 diabetes patients.

Key terms: type 2 diabetes, sitagliptin, sulfonylurea, metformin, pharmacoeconomics, modelling

Introduction

Type 2 diabetes (non-insulin-dependent diabetes, according to ICD-10) is a noninfectious epidemic and one of the most dangerous challenges to mankind in the 21st century. According to data from the International Diabetes Federation (IDF), in 2013 about 382 million people in the world had diabetes; and according to a WHO prognosis, by 2035 this number will grow to 592 million people [2]. Complications from diabetes, including cardiovascular disease, caused 4.8 million deaths in 2012 [3]. Of these, 85–90% were patients with type 2 diabetes. The number of diabetics in Russia, according to the 2012 Registry, exceeded 3.5 million, and 3.2 million of them were patients with type 2 diabetes. According to data from epidemiological studies,

the actual number of patients in our country may be 3–4 times higher [4]. According to Ministry of Health data, the mortality rate from diabetes complications is 6.7 cases per 100,000 persons (9,478 cases); disability from diabetes occurs in 2.1 cases out of 100,000 persons (24,415 cases) [1, 4]. The IDF estimates that in 2010, global expenditures to treat and prevent diabetes amounted to over 376 billion dollars US [2]. Costs for hypoglycaemic therapies were only 9% of all direct costs, and 91% of direct costs were tied to the treatment of diabetes complications [5].

For this reason, developing tactics to treat type 2 diabetics is presently one of the most pressing and complex challenges of modern medicine. However, the contemporary strategy in the fight against diabetes is directed at the most effective forms of prevention, and at controlling the progression of the disease and the risks and expenses associated with treating its complications.

Also, one of the most important factors in choosing a treatment tactic is the economic rationale.

Purpose of the study

To perform a comparative pharmacoeconomic analysis of therapy combinations: sitagliptin with metformin, and sulfonylureas with metformin in patients with type 2 diabetes on metformin monotherapy whose target glycemic goal is not reached with diet and exercise.

Data sources and method of pharmacoeconomic analysis

In the first stage of the analysis, an assessment of the efficacy and safety of the compared drugs was performed; and at the second stage, a calculation was done of the total direct medical expenses associated with hypoglycaemic pharmacotherapy, and also the total expenses to correct side-effects and the need to increase treatment by transitioning to insulin. In the third and final stage, the data from the first and second stages were compared and interpreted using the “budgetary impact” method.

The results of the international, randomised clinical study 024 (Nauck et al., 2007), which was the foundation for predicting clinical outcomes using the JADE model (Chen et al., 2008), served as the primary source of initial information in analysing the efficacy and safety of the drugs. This model took into account the Russian data on contemporary approaches to patient management in clinical practice. The JADE model was developed on the basis of the type 2 diabetes model of the UKPDS research team, with some improvements involving particular uses of the hypoglycaemic agents. In study 024, the sulfonylurea derivative used was Glipizide – a third-generation sulfonylurea derivative with the fewest side-effects, such as hypoglycaemia. Thus, when creating a model for the other sulfonylureas the assumption was made that data on this drug could be transferred to them.

An analysis of direct medical costs (second stage) included: determining the cost of hypoglycaemic pharmacotherapy of the comparator drugs, and an estimate

of the costs associated with the long-term consequences of type 2 diabetes (complications, the need for more intensive therapy, and the transition to insulin), as well as the costs associated with hypoglycaemic episodes. Other cost categories (associated with gastrointestinal side-effects) were not considered in light of their insignificance.

The data on drug costs was based on the state registry of maximum wholesale costs for VED (as of the first quarter of 2014) [9].

Since Janumet was not on the list of VED, the calculation used the package price which the marketing authorisation holder MSD was prepared to register as the maximum wholesale cost in the event it was included on the VED registry (Janumet No. 56 – 1974.6 rubles; Januvia No. 28 – 1894 rubles; per MSD data). To determine the cost of metformin, sulfonylurea derivatives, and insulin therapy, the most common brands with the largest market share according to IMS data were selected. Among the metformins, the largest market share (45%) belonged to Siofor; among the sulfonylureas it was Diabeton (market share 52% for the 60 mg dose No. 30); among the basal insulins it was Lantus SoloSTAR (insulin market share of 22%); and among the short-acting insulins it was Actrapid.

The cost of the drugs was calculated by considering the dosage and prescribed regimen recommended in the instructions for use. If there were several doses (for example, Siofor has 500 mg, 850 mg, and 1000 mg), information was gleaned on the percentage of each product line, and an average weighted value was obtained. To calculate the expenses associated with complications from type 2 diabetes, hypoglycaemic therapy, and transitioning to insulin, data from the first stage were used (efficacy analysis), as well as data on the cost of one complication, hypoglycaemic episode, or one year of insulin therapy according to formula 1:

$$C=N \times P; (1)$$

Where: C – cost associated with one specific consequence (for example, myocardial infarction or level 3 hypoglycaemia);

N – average number of occurrences of a specific consequence (calculated per patient);

P – cost of one occurrence of a specific consequence.

The cost of one episode of hypoglycaemia was calculated using the following assumptions:

- Hypoglycaemia level 1 corresponds to hypoglycaemic episodes in which there is no need for medical care as defined by PN024, or episodes of mild hypoglycaemia according to the definition by Holman et al. (2009) [8].
- Hypoglycaemia level 2 corresponds to hypoglycaemic episodes in which there is a need for medical care in the absence of a clearly serious condition as defined in study 024, or moderate episodes of hypoglycaemia according to the definition by Holman et al. (2009). It was assumed that the cost of moderate hypoglycaemia (middle level) consisted of the cost to call an ambulance, and 3 bed-days in the hospital following the ambulance call and patient transport.
- Hypoglycaemia level 3 corresponds to hypoglycaemic episodes in which there is a need for medical care and a clearly serious condition as defined by study 024, or severe episodes of hypoglycaemia according to the definition by Holman et al. (2009). It was assumed that the cost of moderate hypoglycaemia (middle level) consisted of the cost to call an ambulance, 3 bed-days in the hospital, and one injection of glucagon.

The data on the fees for one bed-day and a call for an ambulance were determined by the fees for the Moscow City Fund for mandatory health insurance.

The data on the cost to treat complications of type 2 diabetes were taken from previously published data (I. I. Dedov, 2010), and were converted to prices for first quarter 2014 (table 1)[7].

A “budgetary impact” analysis was performed to compare the cost data. A hypothetical cohort of patients with type 2 diabetes treated with metformin + sulfonylurea (10,000 patients) was chosen, and an estimate was made of the possible changes to the budget and to clinically significant outcomes from type 2 diabetes with the use of sitagliptin in place of the sulfonylurea derivatives. That is, a situational model was created for budgetary changes caused by transitioning patients from the combination of metformin + sulfonylurea to the combination of metformin + sitagliptin.

Results and discussion

The results of the efficacy analysis included the possibility of macro- and microvascular complications, the time until transition to insulin, and the number of hypoglycaemic episodes.

When looking at the likelihood of developing complications, the drugs were comparable and the differences were insignificant (table – 1)¹. This is associated with the fact that both the sulfonylureas and sitagliptin effectively lower glycosylated

haemoglobin and, consequently, the risk of complications from type 2 diabetes.

The time interval before intensification of therapy and transition to insulin was 6.28 and 5.15 years in the sitagliptin and sulfonylurea groups, respectively.

In the sulfonylurea group, the incidence of hypoglycaemia occurred more often: 6.9 versus 2.8 per patient, although in general at a mild level with no effect on total medical costs. The effect of hypoglycaemic episodes when using antidiabetic therapy first of all is emotionally negative, it makes the patient feel bad, and it pushes the patient to eat more often to avoid the condition, thus causing weight gain.

The cost of hypoglycaemic therapy for one patient was 23,695 rubles for Janumet (fixed combination drug), 25,937 rubles for Januvia in non-combined form with Siofor, and 4,649 rubles for the combination of Diabeton and Siofor (at an average calculated dose).

As can be seen from the data in this stage, the cost of Janumet is 2,242 rubles less than the cost for the non-fixed combination, given that the package price of Janumet is 80.6 rubles higher than the package price of Januvia. The cost of a sulfonylurea is significantly lower (by 19,047 rubles per year), which is natural in a comparison between an innovative drug and drug with generics. Accounting for other types of costs (treatment complications, relieving hypoglycaemic events, transitioning to insulin) over the long-term reduces this difference in costs.

A long-term analysis revealed that using sulfonylurea derivatives caused more hypoglycaemic episodes and a greater likelihood of complications. Also, patients had to transition to insulin sooner because they reached their threshold level for glycosylated hemoglobin (10%), which required intensification of therapy and more cost. For this reason, the costs associated with these events in the sulfonylurea group were higher than in the sitagliptin group: 368,900 rubles versus 212,975 rubles. (Table 1).

The cost summation showed that total medical costs came to 449,927 rubles and 415,385 rubles in the sitagliptin and sulfonylurea groups, respectively (fig. 1).

Furthermore, the medical costs were compared with the data on efficacy and safety, making it possible to reach a preference in favour of the innovational drug. In order to compare the efficacy results with the cost results, a simulation model of budgetary changes for transitioning from a sulfonylurea to sitagliptin was created using a hypothetical cohort (10,000 patients with type 2 diabetes). The results of the simulation model showed that the effect on the components of the budget were as follows (a reduction in the budget indicates a savings, and an increase in the budget indicates increased costs):

- the budget to purchase the drug could increase by 1.9 billion rubles,
- the budget to treat complications could decrease by 11 million rubles,
- the budget for insulin therapy could decrease by 328 million rubles,
- the budget to relieve hypoglycaemic events (this is primarily the budget for emergency medical treatment) could decrease by 1,220 million rubles.
- the summary effect on the budget is 345 million rubles per 10,000 patients over 10 years, which is 7.7% of the total cost of type 2 diabetes in the simulation model cohort. This effect can be considered to be insignificant, since it is less than the range of wholesale prices, value-added tax, and the wholesale markup for drugs listed in the VED, and it is also close to the annual consumer price index in Russia.

In doing this, the following can be prevented:

- 210,000 episodes of level 1 hypoglycaemia;
- 100,000 episodes of level 2 hypoglycaemia;
- 100,000 episodes of level 3 hypoglycaemia;
- 6 cases of ischaemic heart disease;
- 10 cases of myocardial infarction;
- 9 cases of heart failure;
- 9 cases of amputation due to critical blood loss to the extremities;
- 6 cases of blindness;
- 1 case of kidney failure.

Preventing these events may contribute to a growth in the effectiveness of the healthcare system, and may be its indicators.

Conclusions

Thus, the use of sitagliptin with metformin therapy has an insignificant impact on the budget and at the same time prevents complications from type 2 diabetes and adverse events from hypoglycaemic pharmacotherapy.

Given the choice between the non-fixed combination (sitagliptin + metformin) and the fixed combination (Janumet), the preference must be given to the fixed combination due to its lower cost and greater ease of use. Single entity sitagliptin (Janumet) monotherapy is necessary if there are indications for a starting monotherapy, or if metformin is contraindicated or causes serious side effects, and also in patients whose treatment was started not with metformin but with another hypoglycaemic drug.

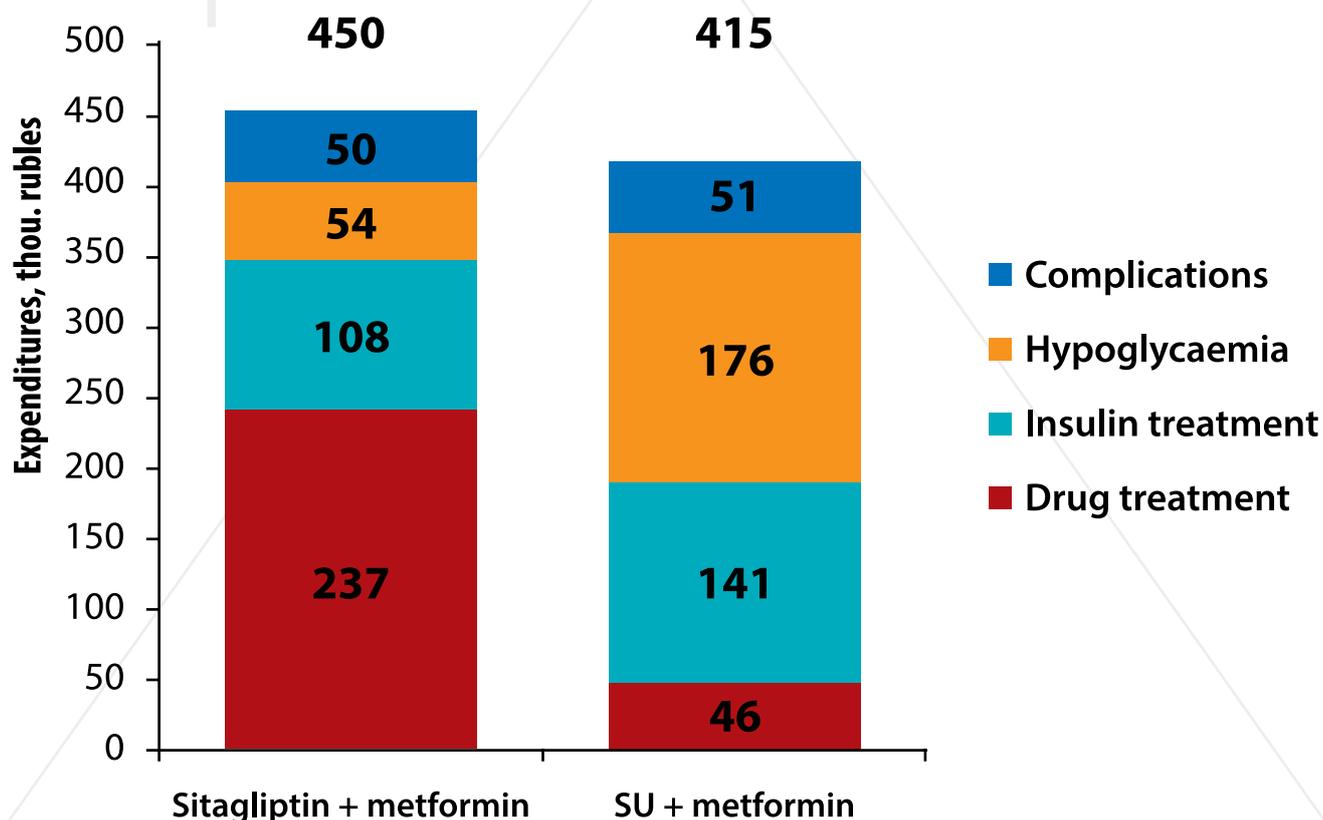
¹ In pharmacoeconomic studies, minor differences in clinical outcomes are most often assessed during a statistical analysis of the sensitivity of the results to changes in the initial data.



Table 1 Initial data on the projected efficacy and safety over 10 years, the cost per unit (one complication, one day of insulin therapy) and

Complications	Projected efficacy and safety		Cost per unit	Costs for all events	
	Sitagliptin+Met	SU+Met		Sitagliptin+Met	SU+Met
Ischaemic heart disease	3,60%	3,66%	260 552 rubles/year	9 380 rubles	9 536 rubles
Myocardial infarction	6,13%	6,23%	417 027 rubles/event	25 564 rubles	25 981 rubles
Congestive heart failure	1,44%	1,52%	27 946 rubles/year	402 rubles	425 rubles
Stoke	1,38%	1,38%	307 446 rubles/event	4 243 rubles	4 243 rubles
Amputation	1,41%	1,50%	450 996 rubles/event	6 359 rubles	6 765 rubles
Blindness	1,57%	1,63%	48 404 rubles/event	760 rubles	789 rubles
Kidney failure	0,68%	0,69%	522 789 rubles/event	3 555 rubles	3 607 rubles
Time before transition to insulin	6,28 years	5,15 years	79,76 rubles/event	108 353 rubles	141 148 rubles
Hypoglycaemia (number of episodes per year)					
Mild (level 1)	1,8	3,9	10 rubles/event	180 rubles	390 rubles
Moderate (level 2)	1	2	5435,96 rubles/event	54 360 rubles	108 719 rubles
Severe (level 3)	0	1	6768,67 rubles/event	0 rubles	67 687 rubles

Figure 1. Total medical costs for 1 patient over 10 years using the combinations: metformin + sitagliptin and metformin + SU



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