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PHARMACOECONOMIC ANALYSIS OF THE USE OF DAPAGLIFLOZIN FOR TREATMENT OF TYPE 2 DIABETES MELLITUS

Kulikov A.Yu., Makarova E.I., Novikov I.V.

Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Moscow, Russia

Summary: *The most dangerous consequences of the global diabetes epidemic are diabetes-related complications. A wide variety of treatment options is currently available for patients with type 2 diabetes mellitus. However, the existing treatments have proven effective for no more than half of diabetic patients who managed to compensate the occurring complications, which is the reason for introducing novel glucose-lowering medicines into practice. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a new class of innovative medicines. Dapagliflozin was the first medicine in this group to be registered on the territory of Russia. Numerous trials have confirmed the efficacy of dapagliflozin at any stage of type 2 diabetes mellitus, both as monotherapy and in combination with metformin, sulfonylureas, dipeptidyl peptidase 4 inhibitors (iDPP-4) and insulin. Thus, the wide range of available glucose-lowering drugs, lack of adequate control over the disease and introduction of novel medicines warrant a new pharmacoeconomic study.*

The purpose of this study was to perform a pharmacoeconomic evaluation of dapagliflozin as a preferential medicine used to treat patients with type 2 diabetes mellitus, as compared to monotherapy or combined use of medicines of the sulfonylureas, metformin, glyptins, glyflozins and insulin group, by means of a cost analysis, and cost-effectiveness and budget impact analysis. Based on the results of the cost-effectiveness analysis, the dapagliflozin treatment scheme was reported to have the lowest cost of type 2 diabetes therapy to quality adjusted life-year (QALY) ratio compared to therapy regimens involving metformin, sulfonylureas, iDPP-4, basal and bolus insulins.

The budget impact analysis demonstrated that treatment using Forxiga would result in budget savings of 31 million rubles over five years, if 1000 patients were to hypothetically switch over from other treatment regimens.

Keywords: *dapagliflozin, type 2 diabetes mellitus, cost analysis, cost-effectiveness analysis, budget impact analysis, pharmacoeconomics, direct costs.*

Introduction

Diabetes mellitus (DM) is a global epidemic of non-infectious nature and one of the most dangerous challenges faced by the world community in the 21st century. According to the State Register of Diabetic Patients, as of the end of 2016, 4.35 million people (three percent of the population) covered by regular medical check-ups in the Russian Federation were diagnosed with DM, and 92% of them had type 2 DM. However, these figures understate the actual number of patients as they include only detected and registered DM cases. According to the findings of a large-scale Russian epidemiological study, type 2 DM is diagnosed only in 50% of all cases. Therefore, the actual number of diabetic patients in the Russian Federation is at least 8-9 million (about 6 percent of the population), which poses an extreme long-term threat, considering that a significant number of patients remain undiagnosed and, consequently, do not receive any treatment and are at high risk of developing vascular complications [1].

Diabetes mellitus is a progressive disease that can lead to the development of multiple complications [5]. The risk of cardiovascular pathology, blindness, lower limb amputations and renal failure is significantly higher for patients suffering from this condition. Most type 2 diabetes mellitus patients have to regularly take multiple medications in order to control the disease and its complications. According to the Ministry of Health, about 15% of the total healthcare budget in Russia is currently being allocated to treatment of diabetes. Over 80% of the budget is spent on diabetic complications treatment. Moreover, unless adequate measures are adopted immediately, the costs are likely to increase dramatically in the near future [1, 18, 19]. Diabetes mellitus causes significant emotional distress and social, as well as serious material, harm, which justifies the search for new and more effective treatment options [3].

One of the most pressing and complex challenges faced by modern health care is to define a therapeutic approach to treatment of type 2 DM patients. An antidiabetic treatment strategy has to be focused on the most effective ways of preventing and controlling the progression of the disease, and should also cover any disease-related risks and costs associated with complications. The combination of the high prevalence of the disease and severity of its economic and social consequences, the wide range of available pharmaceuticals and limited healthcare resources warrants a new pharmacoeconomic analysis.

Compared alternatives and research methods

The purpose of this study was to conduct a pharmacoeconomic evaluation of innovative medicines used to treat patients suffering from type 2 diabetes mellitus by comparing the cost-effectiveness ratios, and safety and quality of life indicators associated with different treatment regimens: monotherapy and combined therapy with dapagliflozin, using dipeptidyl peptidase 4 inhibitors as monotherapy and in combination (fixed and free) with metformin (MET), basal and bolus insulins, combined therapy involving sulfonylureas (SU) and metformin and basal insulins.

Due to the lack of long-term data on the compared therapy schemes, the economic evaluation was performed using the probabilistic Markov switching model, which is built in Microsoft Excel and applied to modeling disease progression and evaluating results according to the QALY terminology. Taking into account the forecast period, the time horizon was set at 5 years and the discount rate was set equal to 3.5 percent.

Table 1 provides a list of medicines that were compared as alternative therapies.

Kulikov A. Yu. tel.: +7(968) 879-88-02, e-mail: 7677041@mail.ru

Table 1. Medicinal products included in the study

Trade name	INN
Glucophage Long	Metformin
Glucophage	Metformin
Siofor	Metformin
Formetine	Metformin
Ongliza	Saxagliptin
Galvus	Vildagliptin
Januvia	Sitagliptin
Tradjenta	Linagliptin
NovoRapid	Insulin aspart
Humalog	Insulin lispro
Apidra SoloStar	Insulin glulisine
Actrapid NM	Insulin soluble
Lantus	Insulin glargine
Levemir	Insulin detemir
Tresiba FlexTouch	Insulin degludec
Forxiga	Dapagliflozin
Janumet	Metformin+Sitagliptin
Galvus Met	Vildagliptin+Metformin
Kombiglyze Prolong	Metformin+Saxagliptin XR
Glucovance	Glibenclamide+Metformin
Maninil	Glibenclamide
Glimepiride (Pharmstandart)	Glimepiride
Amaryl	Glimepiride

Abbreviations: XR – extended release medicine

According to the national clinical guidelines [1] on efficient combinations of medicines used to manage of type 2 DM, the above medicinal products were grouped according to switch regimens for further comparison:

1. iDPP-4 vs dapagliflozin (DAPA);
2. metformin (MET) + iDPP-4 (fixed and non-fixed combinations) vs metformin + dapagliflozin;
3. metformin + SU + basal insulins vs metformin + SU+ dapagliflozin;
4. basal insulins + bolus insulins vs basal insulins + dapagliflozin.

Therefore, the evaluation was structured as comparison of innovative medicines against traditional treatment regimens. To this end, a direct comparison was performed within each group. In line with the stratified strategy of DM management [1], each regimen was linked to a specific level of switching, which made it possible to analyze innovative medicines as elements of various therapy schemes. Trade names for INN groups referring to multiple items were determined based on the pharmaceutical market monitoring data of the IMS Health database. Medicines holding the largest market share in their respective classes were selected as the most relevant alternatives for comparison. Both fixed and free combinations of medicines were included in the analysis for metformin + iDPP-4; an assumption in favor of a fixed combination was made for metformin + SU.

Based on clinical guidelines on medical care provided to diabetic patients [1], as well as information search results, a number of efficacy endpoints were defined to be used as references in pharmacoeconomic evaluation of the above-mentioned alternative therapies. The efficacy endpoints included the QALY indicator, which was to be calculated using data on changes in direct clinical effects (glycated hemoglobin level, body mass index and systolic blood pressure).

Patient profiles with baseline parameters were derived for each treatment regimen from relevant clinical trials. Whenever such information was not publicly available, the profile was built based on UKPDS 33 [11].

A cost analysis was then conducted based on the costs of diagnostics, primary pharmacotherapy and treatment of exacerbations, as well as data on the duration of type 2 DM patients treatment, with a view to assessing total therapy costs in the compared treatment groups.

The next step was to perform a cost-effectiveness analysis with reference to the above-mentioned efficacy endpoints in each compared group.

Further, a budget impact analysis was conducted taking into account the duration of treatment and the number of diabetic patients in each of the Russian regions, in order to assess the potential overall impact on the healthcare budget.

Efficacy analysis

In consideration of the stated purpose of the pharmacoeconomic study, an information search was performed to locate appropriate publications on relevant subjects in the PubMed, Medlink and Cochrane databases. A separate search request was made for each switch regimen, and a specific study was then selected. Search requests were made in such a way, so that the retrieved publications would contain the following keywords, depending on the switch regimen: "dapagliflozin", "metformin", "add-on therapy", "oral antidiabetic agent, dipeptidyl peptidase IV (4) inhibitor or DPP-4 inhibitors", "combination with metformin", "sulfonylurea compounds or sulfonylurea derivative", "long acting insulin or long acting analog or slow acting insulin or slow acting analog", "sodium glucose transporter 2", "monotherapy", "rapid acting insulin or rapidly acting insulin or fast acting insulin or quick acting analog or rapid acting analog or rapidly acting analog", etc. The keywords such as "diabetes", "type 2 or type II", "non insulin dependent diabetes mellitus", "clinical trial", "glycosylated hemoglobin", "systolic blood pressure", "adult", "body mass index" and "meta-analysis" were used in all search requests. The endings were replaced with the * symbol.

In addition, an information search was conducted in the Russian Medicine database of the Central Scientific Medical Library of the I.M. Sechenov Moscow State Medical University and scientific electronic library elibrary.ru, as well as using free search engines (e.g. Yandex, Google, etc.).

The search identified more than 7000 publications as meeting the search request criteria. Duplicate publications and studies not related to the treatment of type 2 DM with glucose-lowering medicines were excluded. Randomized clinical trials comparing medicinal products with placebo, as well as publications on preliminary study results and publications in languages other than English were also excluded from further analysis. Studies were deemed eligible for inclusion if they contained data on HbA1c, systolic blood pressure (SAD) and weight changes, as well as hypoglycemic event rates or quality of life data related to the above-mentioned drug combinations in the results section. The level of evidence was determined according to hierarchy of evidence ranking systems applied to clinical trial results. Studies with A or B level of evidence (evidence summarized in a systematic review or meta-analysis and evidence from prospective RCTs, respectively) were selected above all others. Whenever such studies were unavailable, studies with a lower level of evidence were considered. Finally, 32 publications were included following a detailed analysis screening.

Studies were further selected for each of the switch regimens described above. Preference was given to meta-analyses or direct comparison trials containing information referring to all three efficacy endpoints (changes in weight, HbA1c and SAD), as well as to the hypoglycemic events rate (compared to insulins). The next step was to examine the study horizon, which was to extend to at least 48 to 52 weeks. Whenever studies with such time horizon were unavailable, 24-week clinical trials were included in the analysis, on the assumption that efficacy rates reported at week 24 would correspond to the efficacy measured at week 48 for all medicines concerned. As a result, data on primary efficacy endpoints were obtained based on the studies presented in Table 2. Since the required information was not available for all products compared within this pharmacoeconomic study, the analysis of surrogate efficacy endpoints was based on the following assumptions:

1. efficacy of all iDPP-4 products was the same;
2. efficacy of all basal insulins was the same;
3. efficacy of all bolus insulins was the same;
4. efficacy of glimepiride and glibenclamide was the same;
5. efficacy of the combination of basal and bolus insulins and combined insulins was the same (according to Giugliano D. [12]);
6. efficacy of fixed and free combinations of metformin+iDPP-4 was the same;
7. efficacy of fixed and free combinations of metformin+SU was the same.

The next step in the efficacy evaluation was to measure the QALY endpoint by calculating the number of complications based on surrogate endpoints, such as changes in HbA1c, SAD and weight.

Data of the United Kingdom Prospective Diabetes Study (UKPDS) [9,10,17] were used to assess the impact of primary endpoints on the

prospects of complications developing among type 2 DM patients. The relation between the number of complications and HbA1c, SAD and change in BMI was described in UKPDS 35 [9], UKPDS 36 [17] and a study conducted by Eeg-Olofsson K. at el. [2], respectively. The obtained data were then used to calculate the incidence of complications over 1 year per patient for each regimen compared. After that, the QALY indicator was calculated using a discount rate of 3.5% to evaluate the quality of life over the period of 5 years.

Cost analysis

First, we analyzed the cost of monotherapy involving all compared medicines, with the obtained results further used to calculate the cost of a pharmacotherapy course related to a specific switch regimen. The cost of monotherapy involving medicines included in the VED list was calculated according to the VED registry prices as of June 1, 2016 [7]. For the medicines that were not included in the VED list, auction prices, according to the IMS Health database, were used. The dosage schedule was determined in accordance with Order No. 1581n of the Ministry of Health of the Russian Federation of December 28, 2012 "On approval of standard of primary medical care for insulin-dependent diabetes mellitus patients" [8] (hereinafter referred to as the Standard), effective at the time of the pharmacoeconomic, and Patient Information Leaflets. In addition, the cost of needles (13 rubles per unit) was included in the calculation of the cost of monotherapy involving injection medicines administered with pre-filled syringes.

The obtained results were further used to calculate the cost of a pharmacotherapy course using a specific group of medicines (for example, basal insulins) at weighted average prices, taking into account the respective market share of the medicines according to IMS Health.

To calculate the cost of outpatient treatment, data from the list of diagnosis and treatment services provided to type 2 DM patients according to the current Standard were used, excluding the cost of pharmacotherapy. The cost of medical services was calculated using the rates published by the Federal Compulsory Medical Insurance Fund for Moscow as of 2016. The cost of outpatient treatment amounted to 84,010 rubles, and was the same for all treatment regimens.

As the next step, we calculated the cost of treating complications developing in the first year and their consequences in subsequent years. Based on I.I. Dedov [6], the following conditions were considered as complications developing during subsequent years include: development of diabetic foot (without critical limb ischemia) following a stroke and development of angina following myocardial infarction. Whenever patients reported angina, heart failure or microvascular complications in the first year, they were recorded as having the same complications in subsequent years. Any case of diabetic foot with critical limb ischemia was considered as an amputation. The cost of complications treatment was calculated using the costs of full treatment course according to the Federal Compulsory Medical Insurance Fund for Moscow. Whenever such data were not available, the cost was calculated based on the relevant standards of medical care and service rates published by the Federal Compulsory Medical Insurance Fund for Moscow. At the final stage of the cost analysis, total direct medical and non-medical costs of type 2 DM therapy over 5 years were calculated (Table 3).

Cost-effectiveness analysis

As part of this pharmacoeconomic study a cost-effectiveness analysis per type 2 DM patient was conducted. The QALY indicator was used as an outcome measure. The time horizon was set at five years, and the discount rate was set equal to 3.5 percent (Table 4).

Based on the results of the cost-effectiveness analysis, we can infer that type 2 DM treatment using dapagliflozin is associated with the lowest cost per efficacy unit compared to other treatment regimens involving the use of metformin, sulfonylureas, iDPP-4, basal and bolus insulins. These results suggest a more effective control over complications and, consequently, higher efficacy of the product and lower costs.

Budget impact analysis

The next step of the study involved conducting a budget impact analysis to assess the level of health care budget expenditure corresponding to each treatment regimen. This calculation allows to estimate budget savings resulting from the procurement of different glucose-lowering medicines, taking into account changing market shares referring to the compared alternative therapies in the current and simulated situations. The analysis included the total estimate of type 2 DM treatment costs referring to all treatment regimens. It was assumed for the purpose of the budget impact analysis calculations that it was possible to choose the number of patients to undergo treatment. The number of patients in the modeled situation was set equal to 1000. Market shares were distributed among switch regimens in a way that was most representative of the real situation on the market. All direct medical costs associated with the treatment of diabetes and its complications over 5 years were included in the analysis.

The budget impact analysis thus demonstrated that, if all of the patients (1000) were to switch to type 2 DM treatment regimens involving the use of dapagliflozin, the resulting budgetary savings would amount to 31,542,778 rubles over 5 years (6,308,556 on average per 1 year) - compared to mono- and combined therapy with iDPP-4 and combined therapy with insulins.

Conclusions

The pharmacoeconomic evaluation of dapagliflozin as a pharmacotherapy of type 2 DM established that:

1. According to the efficacy analysis, the use of dapagliflozin (both as monotherapy and in combination with the medicines compared) for treating patients suffering from type 2 DM resulted in greater reductions in glycated hemoglobin, systolic blood pressure and body mass index compared to DPP-4 inhibitors (as monotherapy and in combinations with metformin) or the combination of basal and bolus insulins.

2. The cost-effectiveness analysis revealed that:

- dapagliflozin monotherapy was a dominant therapy compared to saxagliptin, vildagliptin, sitagliptin, linagliptin;
- metformin + dapagliflozin was a dominant therapy compared to fixed and free combinations of metformin + iDPP-4;
- metformin + sulfonylureas + dapagliflozin was a dominant therapy compared to basal insulin + metformin + sulfonylureas;
- basal insulin + dapagliflozin was a dominant therapy compared to basal and bolus insulin therapy.

Table 2. Studies included in the pharmacoeconomic analysis. Results of primary endpoints comparison

Study	Treatment regimen	Δ HbA1c, %	Δ weight, kg	Δ BMI	Δ SAD, mm Hg	Hypoglycemia		
						symptom.	nocturnal	severe
ICON, 2015 [14]	DAPA	-0.70	-1.61	-0.57	-2.96	n/a	n/a	n/a
	iDPP-4	-0.67	0.63	0.22	0.56	n/a	n/a	n/a
Goring, S. M., 2013 [13]	MET + DAPA	-0.92	-2.86	-1.00	n/a	0.0310	n/a	0.0004
	MET + iDPP-4	-0.84	-0.11	-0.04	n/a	0.0460	n/a	0.0005
ICON, 2013 [15]	MET+SU+DAPA	-0.69	-2.40	-0.85	-4.47	0.0102	0	0.0040
	MET+SU+BASAL	-1.08	1.39	0.49	0.85	0.0058	0	0.0020
NMA, 2014 [16]	INS+DAPA	-0.57	-2.04	-0.72	n/a	0.0485	n/a	0.0116
	BASAL+BOLUS	-0.28	1.23	0.43	n/a	0.0626	n/a	0.0196

EMPA - empagliflozin, INS - insulins, BASAL - basal insulins, BOLUS - bolus insulins

Table 3. Cost analysis results

Treatment regimen	Cost of pharmacotherapy, RUB	Cost of medical services, RUB	Cost of complications, RUB	Total cost, RUB
iDPP-4 vs DAPA				
dapagliflozin	112,064	379,310	494,839	986,212
vildagliptin	71,923	379,310	507,197	958,430
linagliptin	80,093	379,310	507,197	966,599
saxagliptin	87,344	379,310	507,197	973,850
sitagliptin	107,296	379,310	507,197	993,803
MET + iDPP-4 (fixed combination) vs. MET + DAPA				
MET + dapagliflozin	130,095	379,310	393,664	903,068
MET + vildagliptin	159,224	379,310	409,353	947,887
MET + saxagliptin XR	208,236	379,310	409,353	996,899
MET + sitagliptin	217,112	379,310	409,353	1,005,775
MET + iDPP-4 (free combination) vs. MET + DAPA				
MET + dapagliflozin	130,095	379,310	393,664	903,068
MET + vildagliptin	89,955	379,310	409,353	878,617
MET + linagliptin	98,124	379,310	409,353	886,787
MET + saxagliptin	105,375	379,310	409,353	894,038
MET + sitagliptin	125,328	379,310	409,353	913,990
MET + SU + BASAL INS vs. MET + SU + DAPA				
MET + SU + dapagliflozin	157,438	379,310	503,048	1,039,796
basal insulin + MET + SU	199,845	379,310	487,351	1,066,506
BASAL + BOLUS INS vs. BASAL INS + DAPA				
basal insulins + dapagliflozin	247,151	379,310	506,805	1,133,266
basal + bolus insulins	206,875	379,310	555,429	1,141,614

Table 4. Results of cost-effectiveness analysis

Treatment regimen	QALY	Total cost, RUB	CER, RUB
iDPP-4 vs. DAPA			
dapagliflozin	3.25	986,212	303,362
vildagliptin	3.15	958,430	304,100
linagliptin	3.15	966,599	306,692
saxagliptin	3.15	973,850	308,993
sitagliptin	3.15	993,803	315,323
MET + iDPP-4 (fixed combination) vs. MET + DAPA			
MET + dapagliflozin	3.30	903,068	273,748
MET + vildagliptin	3.22	947,887	294,423
MET + saxagliptin XR	3.22	996,899	309,647
MET + sitagliptin	3.22	1,005,775	312,404
MET + iDPP-4 (free combination) vs. MET + DAPA			
MET + dapagliflozin	3.30	903,068	273,748
MET + vildagliptin	3.22	878,617	272,907
MET + linagliptin	3.22	886,787	275,445
MET + saxagliptin	3.22	894,038	277,697
MET + sitagliptin	3.22	913,990	283,894
MET + SU + BASAL INS vs. MET + SU + DAPA			
MET + SU + dapagliflozin	3.27	1,039,796	317,789
basal insulin + MET + SU	3.11	1,066,506	343,253
BASAL + BOLUS INS vs. BASAL INS + DAPA			
basal insulins + dapagliflozin	3.25	1,133,266	348,791
basal + bolus insulins	3.08	1,141,614	370,110

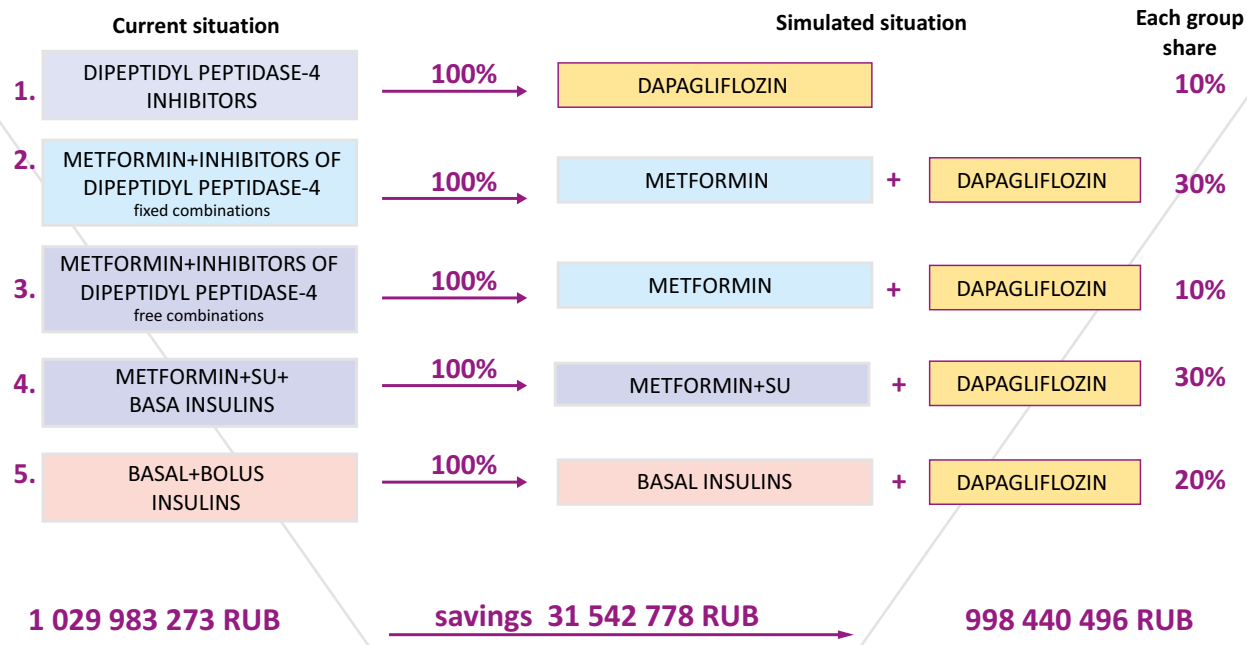

Figure 1. Results of budget impact analysis

3. The budget impact analysis proved that switching 1000 patients (i.e. 100%) to treatment regimens involving the use of dapagliflozin would result in average budget savings of 31 mln rubles over 5 years (6 mln rubles on average per 1 year) of treatment.

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