№1 ^{Том 5}
2017

Фармакоэкономика

теория и практика

Pharmacoeconomics
theory and practice

№1 ^{Volume 5}
2017

- РЕЗУЛЬТАТЫ РОССИЙСКИХ
ФАРМАКОЭКОНОМИЧЕСКИХ
ИССЛЕДОВАНИЙ
- XI НАЦИОНАЛЬНЫЙ КОНГРЕСС С МЕЖДУНАРОДНЫМ
УЧАСТИЕМ «РАЗВИТИЕ ФАРМАКОЭКОНОМИКИ
И ФАРМАКОЭПИДЕМИОЛОГИИ
В РОССИЙСКОЙ ФЕДЕРАЦИИ» –
«ФАРМАКОЭКОНОМИКА 2017»
27-28 МАРТА 2017г., ЕКАТЕРИНБУРГ

ECONOMICAL ADVANTAGES OF INSULIN ANALOGUES USE IN BASAL-BOLUS REGIMEN FOR THE THERAPY OF TYPE 1 DIABETES MELLITUS

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Introduction. According to the first Global Report of the WHO, diabetes mellitus is an important public health problem, one of four priority noncommunicable diseases (NCDs) targeted for action by world leaders. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades [1].

In the estimation of the WHO, 422 million adults were living with diabetes in 2014, compared to 108 million in 1980. The global prevalence (age-standardized) of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population.

Diabetes caused 1.5 million deaths in 2012. Higher-than-optimal blood glucose level (hyperglycaemia) caused an additional 2.2 million deaths by increasing the risks of cardiovascular and other diseases. A high proportion (43%) of these 3.7 million deaths occurs before the age of 70. This parameter is higher in low- and middle-income countries than in high-income countries [1].

The International Diabetes Federation (IDF) predicts that the number of people with diabetes will double by 2025, and the estimated number of people with the disease will have risen to 500 million people by 2030 [2].

According to the State Register of Patients with Diabetes, 3,964,889 patients were registered in Russia as of January 1, 2014. Type II diabetes mellitus is more common, it most often occurs in people who are overweight and physically inactive. There are 339,360 people with type I diabetes mellitus, including 20,373 children, 10,038 adolescents, and 308,949 adults, and 3,625,529 patients with type II diabetes, including 409 children, 342 adolescents, and 3,624,778 adults [3].

In 2016, the academician I.I. Dedov et al. published the results of their study of the economic burden of diabetes for the RF. According to their paper, the average annual treatment cost per patient with type I diabetes mellitus (T1DM) was 81.8 thousand rubles, and per patient with type II diabetes mellitus (T2DM) – 70.8 thousand rubles. At that, medical costs for patients with complications of diabetes are 3 times as high as those for patients without complications, while the costs of drug therapy of the primary condition itself account for 26% only in patients with T2DM. Though the majority of T2DM patients were older than 60 years, non-medical and indirect costs accounted for almost 25% of the economic burden: in patients with T1DM, these costs accounted for 35% of the burden. The structure of medical costs depends on the diabetes type: in T1DM costs were mainly associated with the treatment of diabetes, while in T2DM half of medical costs were associated with the treatment of diabetes, and the other half – with the treatment of diabetes complications. Medication costs accounted for 69%, and hospitalization costs – for 22% of medical costs for T1DM patients. The results of regression analysis showed that the strongest predictors of medical costs growth in diabetes were the number of hospitalizations, presence of complications and insulin therapy [4].

In spite of the growing demand and a high level of diabetes incidence in Russia, insulin consumption in this country is the lowest among all European countries and accounts for 39 units per citizen. As to other countries, these parameters equal 125 units in Poland, 200 – in Germany and 257 units – in Sweden, respectively [5].

The main principle of insulin therapy in T1DM is to get as close as possible to the physiological level of insulin secretion in healthy people [6]. Physiologically, insulin secretion can be divided into basal and stimulated (postprandial) ones. Basal secretion ensures optimal level of glycaemia during the interprandial phases and the overnight fast, facilitating utilization of glucose that forms in the body in between meals (gluconeogenesis, glycolysis). Insulin secretion after a meal conforms to the level of postprandial glycaemia, i.e., depends on the amount of carbohydrates consumed. The intensified basal-bolus insulin therapy regimen at present is considered the optimal regimen for all T1DM patients and is the closest to the physiological insulin secretion level. This regimen requires once or twice daily injections of a long-acting insulin (basal analogue or NPH insulin) and use of short-acting insulin (insulin regular or a fast-acting analogue) with every meal (usually 3–4 times a day).

Invention of analogues provided patients and physicians with additional benefits [6, 7]. Basal analogues are associated with lower risk of hypoglycaemia and higher patient satisfaction with therapy. Their advantages are most prominent in children and adolescents, people with brittle diabetes who can't achieve glycaemic control with NPH insulin and in patients with a history of frequent hypoglycaemia. Ultra-short-acting insulin analogues are more convenient for patients, as they can be injected right before or after a meal, which allows for a more flexible dietary regimen and diet. Their use decreases the risk of hypoglycaemia and improves glycaemic control.

Their higher cost is the only barrier to their wide use. Moreover, there are too few evidence-based studies that directly compare genetically engineered and analogue insulins to give a complete assessment of both quantitative (associated with costs), or qualitative advantages of the latter [7].

PREDICTIVE was a multicenter, multi-national, observational study initially intended to assess the safety and efficacy of insulin detemir in patients with diabetes [8, 9]. The European cohort included 20,531 patients with diabetes (7,420 with T1DM) from 11 countries. A subgroup of 4,782 T1DM patients was switched from a basal-bolus regimen with NPH insulin (3,117 patients) or insulin glargine (1,665 patients) to insulin detemir basal-bolus therapy. Another subgroup of patients with human insulin basal-bolus regimen with NPH insulin ($n = 570$) was switched to insulin detemir/insulin aspart basal-bolus regimen (Levemir®/NovoRapid®). Mean follow-up was 14.4 weeks. The primary endpoint was the number of serious adverse drug reactions (SADRs), including number of severe hypoglycaemia episodes. Secondary endpoints were: number of overall and nocturnal hypoglycaemia episodes; glycated hemoglobin (HbA1c); fasting glucose; glycaemia variability; and change in body weight. Serious adverse drug reactions were reported by 2.0% patients previously receiving NPH insulin, 2.7% patients previously receiving insulin glargine and 1.2% patients previously receiving human basal-bolus insulins. Severe hypoglycaemia incidence was significantly reduced in NPH insulin (by 55%), insulin glargine (by 51%), and human basal-bolus insulin groups (by 54%; $p < 0.0001$ for all). HbA1c was reduced by 0.5%–0.4%–0.6% in the three groups, respectively. Mean fasting glucose and within-patient fasting glucose variability significantly decreased in all groups. Body weight remained stable. Thus, insulin detemir (Levemir®) and insulin aspart (NovoRapid®) basal-bo-

lus therapy was demonstrated to improve glycaemic control and reduce hypoglycaemia with weight neutrality.

Taking into consideration the urgent character of the problem for the RF, where approximately 40% of the total number of people with diabetes receives life-long insulin therapy, we studied economic consequences of basal-bolus therapy modification with consideration of domestic clinical practice peculiarities [4].

The purpose of our study was to conduct a pharmacoeconomic analysis of the use of a basal-bolus therapy regimen with insulin detemir/insulin aspart compared to the traditional regimen of NPH insulin–Actrapid for the treatment of patients with type 1 diabetes mellitus in the RF.

Materials and methods

Results of the PREDICTIVE study (2008) were the source of data on efficacy and safety of various basal-bolus insulin therapy regimens [8,9]. The following analyses were performed in the pharmacoeconomic study: cost-effectiveness, cost-benefit and budget impact [10–12].

For the purpose, the most commonly used forms of insulins were chosen in accordance with the treatment regimens – Levemir®/NovoRapid® and Protaphane®/Actrapid®. Only direct medical costs of insulin therapy and treatment of severe hypoglycaemia were analyzed. Drug prices were taken from official sources: State Register of Manufacturers' Maximum Selling Prices of Medicinal Products from the Vital and Essential Drugs List (as of November 1, 2016) [13]. Daily dose of the insulins conformed to the «standard of specialized healthcare in insulin-dependent diabetes mellitus» [14].

Assessment of treatment costs included the following: costs of ambulance call-out with patient transportation, single injection of glucagon, and hospital stay [15].

Costs were assessed per patient in 2016 (366 days) and were related to the «willingness-to-pay margin» in the RF in 2016. [16,17].

Results

Literature review and analysis of PREDICTIVE materials [8,9] determined the basic criteria of efficacy and safety that were then used to perform economic calculations (Table 1).

Table 1. Basic efficacy and safety parameters in the PREDICTIVE study [8,9]

Parameters	Groups		Δ
	P-A	L-N	
Safety – hypoglycaemia (episode/patient/years)			
Severe	3.51	0.52	2.99
Efficacy			
HbA1c level, %	8.1	7.6	0.5
Fasting glucose, mmol/L	9.5	7.9	1.6
Glycaemia vari- ability, mmol/L	2.7	1.9	0.8

Table 3. Insulin therapy costs

BN	U in a package	price of a package, RUR	price of a unit, RUR	daily dose, U	price per day, RUR	price per year, RUR	price of comb. therapy, RUR
Actrapid HM Penfill	1,500	699.92	0.47	40	18.66	6,831.22	11,954.41
Protaphane HM Penfill	1,500	699.89	0.47	30	14.00	5,123.19	
NovoRapid FlexPen	1,500	1,606.88	1.07	40	42.8	15,664.8	34,996.63
Levemir FlexPen	1,500	2,263.68	1.51	35	52.82	19,331.83	

Table 1 demonstrates that Levemir®/NovoRapid® (L-N) regimen achieved more effective control of glycaemia as shown by the decrease of glycated hemoglobin (HbA1c) levels, fasting glucose, and within-patient fasting glucose variability compared to the traditional Protaphane®/Actrapid® regimen. Moreover, «new insulins» have a clearly more favorable safety profile that decreased the number of severe hypoglycaemia episodes.

Prices on various insulins used in the study are shown in Table 2. Insulin analogs (aspart and detemir, Levemir®/NovoRapid®) are shown to cost almost twice as much as the traditional ones [13].

Table 2. Maximum selling prices for insulins [13]

INN	BN	Dosage form, dosage, packaging (full)	UNITS in a pack.	Price, RUR
Soluble insulin [human genetically engineered]	Actrapid® HM Penfill	100 IU/mL solution for injection, 3 mL – cartridges (5) – blisters – cartons	1,500	699.92
Insulin isophane [human genetically engineered]	Protaphane® HM Penfill	100 IU/mL suspension for subcutaneous injection, 3 mL – cartridges (5) – blisters – cartons	1,500	699.89
Insulin aspart	NovoRapid® FlexPen	100 U/mL solution for IV and SC injection, 3 mL – multidose disposable pens (5) – cartons	1,500	1,606.88
Insulin detemir	Levemir® FlexPen	100 U/mL solution for SC injection, 3 mL – multidose disposable pens (5) – cartons	1,500	2,263.68

Costs of insulin therapy for each component individually and the combination per patient-year (366 days for 2016) are shown below. Daily dose of rapid-acting insulins (NovoRapid® and Actrapid®) complied with the standard and was 40 U, of insulin Protaphan® – 30 U, of insulin Levemir® – 35 U, respectively (Table 3) [14].

Costs per patient in Levemir®/NovoRapid® (L-N) regimen are shown to be more than twice as high as those in Protaphane®/Actrapid® (P-A) regimen – 34,996 and 11,954 RUR, with the total difference of 22,042 RUR, respectively.

Cost structure for the treatment of severe hypoglycaemia is shown below in Table 4. Average cost of treating one patient with a severe hypoglycaemia episode is 17,731 RUR.

Table 4. Costs of treating a severe hypoglycaemia episode (RUR), according to the rates of Moscow City Foundation of Mandatory Health Insurance [15,18]

Services	price, RUR	frequency	costs, RUR
Non-specialized ambulance call-out	4,806	1	4,806
Glucagon injection	760	1	760
Bed-day	2,433	5	12,165
Total costs, RUR	17,731		

Table 5 contains total costs in the two treatment groups. The analysis took into consideration the fact that the average number of episodes of severe hypoglycaemia (that required medical assistance and hospital admission) was 3.51 per patient in the P-A group, and 0.52 – in the L-N group, respectively.

Table 5. Total costs in the two groups (RUR)

Parameters	Group		Cost difference
	Protaphane – Actrapid (P-A)	Levemir – NovoRapid (L-N)	
Insulins	11,954	34,997	+ 23,043
Hypoglycaemia	62,236	9,220	- 53,016
Total		74,190 44,217 - 29,973	

Table 5 shows that in spite of the initially high cost of insulin therapy in the L-N group (Levemir®/NovoRapid®), absence of severe hypoglycaemia leading to substantial costs to the healthcare system contributed to total savings of 40.4% (29,973 RUR) in the group compared to the P-A group (Protaphane®/Actrapid®).

During the «cost-effectiveness» analysis, the incremental cost-effectiveness ratio ICER was calculated. It represents the incremental cost associated with 1 additional unit of effectiveness and/or safety (Δ) that was determined by a comparative analysis of the two basal-bolus insulin therapy regimens [16].

The incremental cost of insulin therapy in our study was 23,043 RUR. Analysis results are shown in Table 6.

Table 6. «Cost-effectiveness» analysis results with consideration of the «endpoints» of the PREDICTIVE study [8,9,16]

Parameters	Δ	ICER, RUR
<i>Safety – hypoglycaemia (episode/patient/years)</i>		
Severe	2.99	7,707
<i>Efficacy</i>		
HbA1c level, %	0.5	46,086
Fasting glucose, mmol/L	1.6	14,402
Within-patient fasting glucose variability, mmol/L	0.8	28,804

Thus, Table 6 demonstrates that switch to a new treatment regimen requires additional 46,086 RUR to decrease HbA1c level by 1%, 14,402 RUR – to decrease fasting glucose by 1 mmol/L and 28,804 RUR – to decrease within-patient fasting glucose variability by 1 mmol/L. Prevention of 1 episode of severe hypoglycaemia costs 7,707 RUR per patient-year.

In the «cost-benefit» analysis, we used foreign literature that characterize the change of the utility characteristic – QALY (quality adjusted life years) at development with some diabetes complications or side effects of its treatment [19]. Considering the fact that the two studied treatment groups were originally in one homogeneous cohort (NPH insulin) with comparable demographic and anthropometric data, with similar number of complications and the same treatment regimen, we suggested that their initial QALY was identical (basic utility is 0.8). The later decrease of QALY (during the study) was due to the difference in hypoglycaemia frequency. Change in body weight observed in the groups throughout the study, did not reach «the sensitivity threshold» for QALY (3-5%) and did not affect its values.

The decrease in the utility value in hypoglycaemic state is mainly due to anxiety and fear of such episodes. According to M. Evans et al. (2013), on average, each episode of severe hypoglycaemia leads to the decrease of the utility value (QALY) by 0.0565 [20].

In our study, the average number of severe hypoglycaemia episodes in the P-A (Protaphane-Actrapid) regimen was 6.4 per patient-year that demonstrated the decrease in QALY: $0.0565 \times 3.51 = 0.1983$.

In the L-N (Levemir-NovoRapid) group, where the average frequency of severe hypoglycaemia was 2.9 episodes, QALY decrease was: $0.0565 \times 0.52 = 0.0294$.

The difference in the parameter (Δ QALY) between the two groups was: $0.1983 - 0.0294 = 0.1689$, respectively.

Further, we calculated the «cost-utility» parameter (ICUR), using the formula: [14]

$ICUR = ICER / \Delta QALY$, where ICER – additional costs, RUR; $\Delta QALY$ – the value of the incremental utility parameter.

$ICUR = 23,043 / 0.1689 \approx 136,430$ RUR per QALY

The parameter was assessed with consideration of the «willingness-to-pay margin» (WTPM) calculated in accordance with the WHO recommendations (3-fold GDP at purchasing power parity per capita) [17].

According to the International Monetary Fund data for 2016, the estimated GDP for the RF will be 25,186 US dollars that is 1,556,495 RUR, translated into rubles at the Central Bank of the RF exchange rate (61.8 RUR for 1 US dollar). WTPM for the RF will be 4,669,485 RUR. Therefore, calculated incremental costs are acceptable considering the WTPM for the RF [17,21].

During the budget impact analysis, economic benefit and missed opportunities value were calculated [12].

Annual economic benefit provided by the use of a certain insulin therapy regimen was calculated by the formula:

$CMA = DC_1 - DC_2$ where: CMA – difference of the compared interventions;

DC_1 – direct costs for the P-A treatment regimen; DC_2 – direct costs for the N-A treatment regimen.

$CMA = 74,190 - 44,217 = 29,973$ RUR.

The Levemir®/NovoRapid® (L-N) regimen was demonstrated to save 29,937 RUR per patient-year compared to the Protaphane®/Actrapid® regimen.

The value of missed opportunities at treatment with a more costly MP (Q) was calculated by the formula: $Q = (CMA/C_{low}) \times 100\%$ where Q – % of missed opportunities; CMA – economic benefit; C_{low} – costs of therapy with a less expensive treatment regimen (L-A). $Q = 29,973 / 44,217 = 0.678$ or 67.8 %.

Therefore, patient switch to the basal-bolus regimen of the treatment with Levemir® and NovoRapid® insulins from the human insulins regimen was demonstrated, with consideration of prevented severe hypoglycaemia episodes, to be able to treat additional 67.8% of T1DM patients.

Conclusion

Literature review has demonstrated that basal-bolus therapy with modern insulins Levemir® and NovoRapid® leads to a significant improvement in the glycaemic profile and is associated with a decrease in the frequency of

severe hypoglycaemic state, without any changes in the body weight of type 1 diabetes mellitus patients.

The incremental cost of insulin analogs therapy at the use of the treatment regimen is 23,043 RUR per patient-year, compared to the standard basal-bolus therapy with Protaphane® and Actrapid®. Prevention of 1 episode of severe hypoglycaemia costs 7,707 RUR for the same period, while management of such an episode is 230% more expensive, 17,731 RUR, respectively.

Less frequent severe hypoglycaemia episodes associated with the use of Levemir®/NovoRapid® lead to substantial savings of 29,937 RUR per patient-year, which will allow to treat 67.8% more type 1 diabetes mellitus patients.

Improving of patients' quality of life due to less frequent hypoglycaemia with the treatment of Levemir®/NovoRapid® was accompanied by incremental value of the «cost-benefit» parameter of 136,430 RUR per 1 QALY, which is acceptable, considering the «willingness-to-pay margin» for the RF in 2016.

This research was done on the initiative of the authors with the support of Novo Nordisk. The company has no influence on the choice of studies for the analysis, as well as analysis and interpretation of the results.

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