№2 Том4 2016

Фармакоэкономика
теория и практика

Pharmacoeconomics
theory and practice

№2 Volume4 2016

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PHARMACOECONOMIC ANALYSIS OF TELAVANCIN USE IN RUSSIAN HEALTHCARE SYSTEM FOR TREATMENT OF PATIENTS WITH NOSOCOMIAL PNEUMONIA.

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Abstract
It is the first time a comparative pharmacoeconomic analysis of telavancin (Vibativ®) use for treatment of patients suffering from nosocomial infections caused by resistant bacterial flora using the example of patients with nosocomial pneumonia was performed in Russia. The study was carried out using mathematical modelling with a one-month horizon. Cost-benefit analysis, budget-impact analysis, and sensitivity analysis were used. The study found that telavancin use showed high clinical efficacy and one of the best safety profiles among other medical treatment technologies for such groups of patients. Telavancin use makes economic sense in terms of cost-efficacy ratio as compared to vancomycin and linezolid. According to the results of analysis of budget impact, for wide use estimated strategy requires additional investment to the extent of 13% when compared with the strategies of the use of vancomycin and linezolid.

Key words: *nosocomial pneumonia, pharmacoeconomics, telavancin*

Rationale

About thirty thousand cases of nosocomial infections (NI) are reported in the Russian Federation (RF) annually [1-3]. Bacteria of the *Staphylococcus* genus (*S.aureus)* still remain one of the most common causative agents of NI [4]. The epidemiological situation is complicated by wide spreading of bacteria resistant to oxacillin and methicillin (oxacillin-resistant *Staphylococcus aureus* (ORSA) and methicillin-resistant *Staphylococcus aureus* (MRSA) in hospitals. In Russia, the rate of isolation of *S.aureus* in hospitals is 75.0% of all gram-positive pathogens, and more than half of them are methicillin-resistant [5]. Nosocomial pneumonia (hospital-acquired, NP) is also among the most common NI in Russia and worldwide [6-12]. Telavancin is the first representative of the new generation of glycopeptide antibiotics, semi-synthetic lipoglycopeptides [13-17]. Clinical studies have demonstrated the effectiveness of telavancin in NP patients [18;19].

Objective

To determine the pharmacoeconomic sense of telavancin use for treatment of patients with nosocomial pneumonia from the standpoint of the state healthcare system and the standpoint of a patient in Russia.

Methods

The methodology of clinical and economic analysis utilized industry-specific standards "Clinical and Economic Study" used in the RF and expert guidelines [20-24]: cost-effectiveness analysis (CEA) with calculation of the corresponding coefficient (cost-effectiveness ratio, CER); incremental analysis with calculation of the corresponding coefficient (incremental cost-effectiveness ratios, ICERs). Additionally, a budget-impact analysis with a one-year and three-year horizon was performed [25]. Investigator's standpoint: Russian healthcare system. Study basis: pharmacoeconomic modeling.

Characterization of costs and effectiveness indicators. Costs. Direct costs (DC) were listed: underlying disease (NP) treatment cost—cost of antibacterial medicinal products (MP); cost of treatment aimed at correction of adverse events (AE) caused by MP for the treatment of the underlying disease; cost of laboratory and instrumental investigations, and inpatient and outpatient treatment; treatment cost when therapy with MP of the strategies under consideration is ineffective. Indirect costs (IC) were listed as well: patient's lost earnings owing to temporary disability; outlay of the Social Insurance Fund on temporary disability benefits; lost profits determined as lost gross regional product (GRP). Costs were estimated on the basis of public data [26-29].

Treatment effectiveness. The effectiveness criterion used was efficacy, assessed from the results of randomized clinical studies (RCS) and meta-analyses. Effectiveness criteria included: clinical recovery rate—resolution of clinical symptoms of the infection, %; microbiological response rate—clearing of an infectious nidus from the pathogen; multiple negative bacterial flora tests of biosubstrates, %.

Treatment efficacy was evaluated among the strategies the use of drugs, shown with nosocomial pneumonia caused by multidrug-resistant gram-positive flora: telanvancin, vancomycin and linezolid. Studies with simultaneous inclusion of all three drugs were found by us in connection with this indirect comparison of the data was performed according to the selected performance criteria based on RCTs with comparable populations of patients for demographic, somatic status and the type of pneumonia [19, 30, 33].

Model structure. A model of rendering aid to a NP patient was made [19;30; 31].

Model of decision analysis for evaluation of pharmacoeconomic effectiveness of the medical aid strategies under consideration in nosocomial pneumonia [32]. Modeling started with the choice of an MP for NP therapy: telavancin 10 mg/kg/day; vancomycin 2 g/day; linezolid 1,200 mg/day. The therapy was considered effective if a patient achieved clinical and microbiological recovery following the course of treatment with one of the MP during their hospital stay, or ineffective otherwise. The duration of modeling was 30 days (1 month). In the case of therapy ineffectiveness, it was

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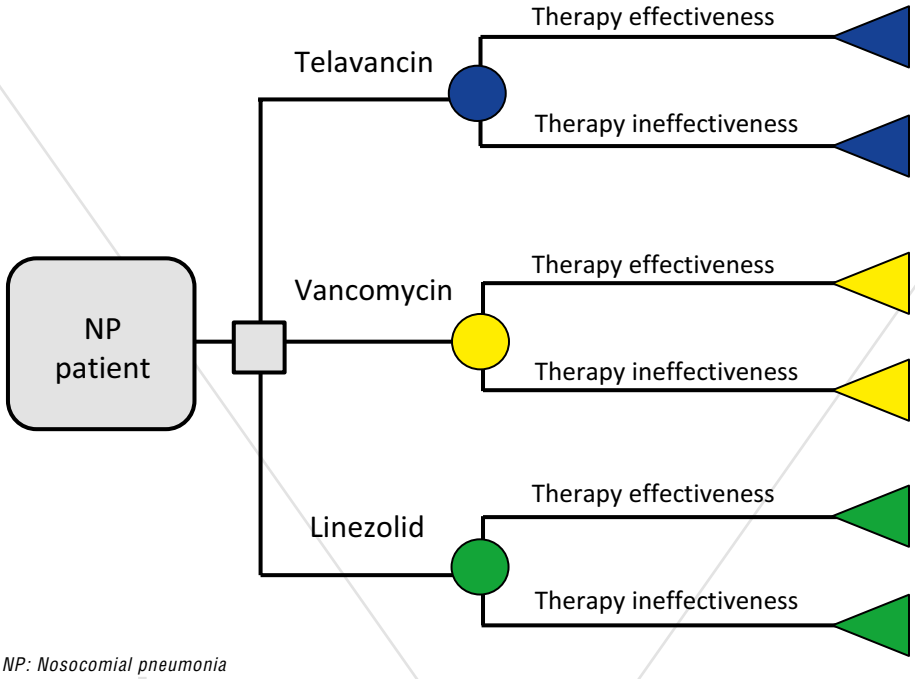
assumed that a patient would develop a septicemic condition that requires further treatment in an intensive care unit (ICU) and initiation of a different antibacterial therapy. A schematic representation of a decision tree model for a NP patient model is given in Fig.1.

Calculation of medical aid cost in different strategies. The calculations are based on the data from standards of financial outlay per medical aid volume unit [27] and the General Tariff Agreement (GTA) for 2016 [25]. Calculation of MP cost in the strategies under comparison is given in Table 2.



NP: Nosocomial pneumonia

Fig.1. Model of decision analysis for evaluation of pharmacoeconomic effectiveness of NP therapy with medicinal products of the strategies under consideration.

Additionally, the probability of development of various AE associated with the therapy strategies under consideration including the cost of medical aid to correct them was evaluated.

Data sources for mathematical modeling

An estimation model determined the cost of disease, probability of development of various events in different strategies of therapy for NP patients—effective and ineffective treatment rates, and complication rates. Table 1 summarizes indicators of therapy effectiveness in patients with disorders under consideration.

Table 1. Effectiveness indicators of the strategies under consideration [18;19;30;31;33]

Effectiveness indicators	Telavancin	Vancomycin	Linezolid
NP			
Clinical recovery rate, %	86,0	75,0	80,1

NP: Nosocomial pneumonia

Cost of medical aid strategies for NP patients. The cost of treatment of the underlying disease (NP) includes outlay on the therapy with MP of the strategies under consideration and outlay on other medical and diagnosis measures, provided for as part of in-hospital stay in accordance with the corresponding diagnosis-related group (DRG) tariff ("Pneumonia, severe" and "REHAB Pneumonia, protracted, resolving (after day 18 from treatment initiation"). Additionally, the intensive care unit stay was included as DRG "Resuscitation of Category 3 complexity (4 to 5 days inclusive)".

Table 3. Total cost of NP treatment with the strategies under consideration

Outlay list	Telavancin	Vancomycin	Linezolid
Outlay on pharmacotherapy per month, RUB	215 600,00	25 970,70	92 008,56
Outlay on hospital aid, RUB	170 622,20		
Total, RUB, 30 days of therapy	386 222,20	196 592,90	262 630,76

Table 2. Cost of therapy with medicinal products of the strategies under consideration

Therapy strategy	Medicinal products (INN)	Trade names	Presentation	Price/ package (RUB)	Course cost
NP					
Telavancin, 10 mg/day, 21 days	Telavancin	Vibativ®	lyophilisate for solution for infusion, 750 mg, vial (1)	11 000,00	215 600,00
Vancomycin, 2 g/day, 21 days	Vancomycin	Edicin®	lyophilisate for solution for infusion 1.0 g, vials (1)	618,35	25 970,70
Linezolid, 1,200 mg/day, 21 days	Linezolid	Zyvox®	solution for infusion 2 mg/ml, 300 ml, single-use infusion bags (10)	21 906,80	92 008,56

INN: International nonproprietary name; NP: Nosocomial pneumonia

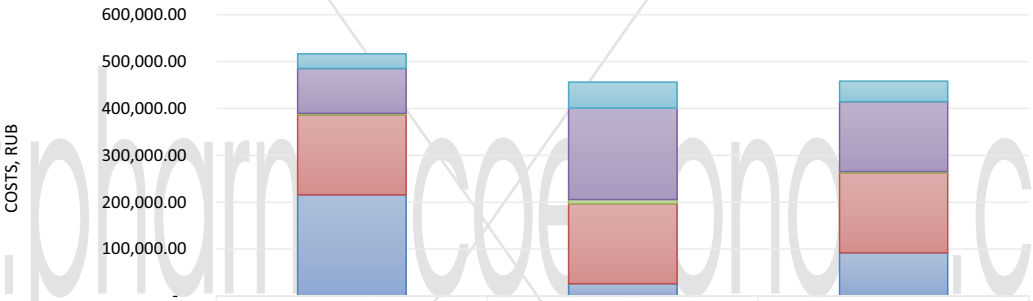
Cost of ineffective therapy. Cost of ineffective therapy with medical aid strategies for NP patients. In the case when any of the NP therapy strategies under consideration proved ineffective, it was assumed that a patient would develop a severe septicemic condition that requires further long-term therapy in an ICU and initiation of a combination antibacterial therapy against gram-positive and gram-negative bacteria. Thus, the cost of ineffective therapy consists of the cost of medical aid under the corresponding DRG in an intensive care unit and the cost of antibacterial therapy. Outlay on antibiotic therapy was calculated as the average cost of medicines against resistant gram-positive flora and a course of broad-spectrum MP, including anaerobic, carbapenems.

Indirect costs. Indirect costs were calculated only for the patients in whom the use of the strategies under consideration proved ineffective and required prolongation of in-hospital stay, and indirect costs covered the entire number of days of disability [34;35].

Cost of medical aid in the case of AE development. Cost of therapy aimed at correction of AE associated with MP used for the treatment of disorders under consideration consisted of the cost of medical and diagnosis measures that are provided for in the case various complications of pharmacotherapy develop, as established in the GTA [28] under the corresponding nosology or clinical condition.

Results

The main scenario assessed the cost of each of the treatment strategies for patients of the target group. All strategies under comparison were modeled over a one-month time horizon. The results obtained are presented in Fig. 2.



	Telavancin	Vancomycin	Linezolid
Indirect costs	30,898.38	55,175.69	43,919.85
Ineffective therapy	95,961.78	195,063.99	148,700.16
AE	3,203.84	9,093.02	3,002.94
Hospital aid	170,622.20	170,622.20	170,622.20
MP	215,600.00	25,970.70	92,008.56

Fig.2. Total DC of treatment with the strategies under comparison calculated per patient, one-month modeling horizon.

As demonstrated by the data given in Fig. 2, the highest cost over a one-month modeling horizon was in telavancin strategy: RUB 516,286. The total costs of linezolid use were only 11.2% lower and constituted RUB 458,253 per patient. The lowest cost was that of vancomycin strategy, which totaled to RUB 455,925. At the same time, the greatest difference was primarily explained by difference in the cost of pharmacotherapy and outlay on ineffective therapy. For example, MP costs component in telavancin group was equal to RUB 215,600, while the same costs constituted RUB 25,970 in vancomycin group, which is 8.3 times lower. MP costs in linezolid group were 2.3 times lower than telavancin costs and totaled to RUB 92,008. At the same time, telavancin and linezolid strategies demonstrated the lowest costs of AE management, RUB 3,203 and RUB 3,002, respectively, on average per patient. Despite the lowest costs of the MP itself, indirect costs, costs of ineffective therapy, and AE management costs were the highest in vancomycin group compared to other strategies.

In general consideration of the strategies, the percentages of therapy costs components differed between the groups of MP under consideration. For example, the MP itself was the main component of DC in telavancin group (41%), while the largest outlay in linezolid group was on hospital aid (37%), and 5.7% of total costs accounted for the MP itself. In vancomycin group, the largest outlay was on ineffective therapy (42%). The share of costs of ineffective therapy was the smallest in telavancin group (18%).

The incidence of various AE was assessed in the treatment groups over the observation period. Such AE as nausea, renal function impairment, and anemia were more common in telavancin group. At the same time, vancomycin strategy was associated with the highest number of AE, and such AE as pancreatitis, paresthesia, diarrhea, thrombocytopenia, polyneuropathy, hypokalemia, and cardiac arrest occurred more commonly in that product group.

The effectiveness criteria were the clinical recovery rate (%) and microbiological response rate (%). In terms of clinical recovery rate, telavancin strategy possessed a higher effectiveness compared to other treatment strategies: the corresponding value was 86%. This value was somewhat lower, 80.14% for linezolid strategy. Vancomycin strategy demonstrated the lowest effectiveness at 75%. Also, it should be noted that telavancin group had the smallest share of patients with prolonged in-hospital stay compared to other treatment strategies. The results of ICER calculation are given in Table 4.

As demonstrated by the data given in Table 4, telavancin strategy for treatment of NP patients was more expensive compared to linezolid and vancomycin strategies, but the effectiveness increased. Compared to vancomycin, the costs increment was RUB 60,360 with effectiveness increment equal to 11% for clinical recovery rate. The corresponding coefficient, ICER, was equal to RUB 548,732 for telavancin strategy, which is 2.4 times lower than the society's willingness-to-pay threshold of RUB 1,341,308. In the same way, the costs increment was RUB 58,032, with effectiveness increment of

Table 4. ICER calculation for the strategies under comparison (clinical recovery rate).

Strategy	DC, RUB	DC increment, RUB	Effect	Effectiveness increment	ICER
Telavancin	516,286.20	60,360.61	86.00%	11.00%	548,732.85
Vancomycin	455,925.59		75.00%		
Telavancin	516,286.20	58,032.49	86.00%	5.90%	983,601.53
Linezolid	458,253.71		80.10%		

5.9% for clinical recovery rate compared to linezolid. The corresponding coefficient, ICER, was equal to RUB 983,601 for telavancin strategy, which is 26% lower than the society's willingness-to-pay threshold of RUB 1,341,308. Thus, it can be concluded the use of telavancin strategy makes economic sense when compared to other treatment strategies for NP patients from the viewpoint of the cost-effectiveness ratio. Sensitivity analysis was performed for the purpose of testing the analysis results if the input parameters are changed.

Probabilistic sensitivity analysis. In simultaneous multiple changes of such parameters as effectiveness and MP costs, telavancin strategy remained the most effective and the most expensive strategy compared to vancomycin and linezolid strategies. The results of the sensitivity analysis confirm the conclusions obtained in the main scenario.

Budget-impact analysis. Total costs of use of telavancin, vancomycin, and linezolid for treatment of NP patients were calculated. The calculation included direct costs linked to the use of the strategies under comparison and indirect costs. The calculation took into account the effectiveness of each strategy. The difference in total direct costs was defined as a saving associated with the use of this or that strategy. The number of patients the saved amount could be spent on was calculated as well. The outlay per patient is RUB 516,286 for telavancin and RUB 455,926 for vancomycin. Linezolid costs are equal to RUB 458,254. Table 5 gives the results of comparison of total DC of the treatment strategies under comparison. The outlay on treatment of 1,000 patients with different strategies was calculated, and three variants were considered where 100%, 60%, and 30% of patients receive the product under consideration.

Таблица 5. Сравнение суммарных затрат в терапии больных с нозокомиальной пневмонией.

Therapy under consideration	100% of patients receive the therapy	60% of patients receive the therapy	30% of patients receive the therapy
	Total costs in RUB		
Telavancin	51,628,620	30,977,172	15,488,586
Vancomycin	45,592,559	27,355,535	13,677,768
Linezolid	45,825,371	27,495,223	13,747,611
Saving in Telavancin use compared to:			
Vancomycin	-6,036,061	-3,621,637	-1,810,818
Linezolid	-5,803,249	-3,481,949	-1,740,975
Additional number of patients treated with telavancin if the budget is equal to telavancin use			
Vancomycin	-	-	-
Linezolid	-	-	-

As demonstrated by Table 5, telavancin use requires additional investments in the amount of up to RUB 6,036,061 from the viewpoint of budget-impact analysis compared to vancomycin and linezolid strategies.

Discussion

It is the first time a comparative pharmacoeconomic analysis of telavancin (Vibativ®) use for treatment of patients suffering from NI caused by resistant bacterial flora using the example of patients with nosocomial pneumonia was performed in Russia. Three medical technologies of NP treatment were evaluated: telavancin at 10 mg/kg/day; vancomycin therapy at 2 g/day; linezolid treatment at 1,200 mg/day. The highest DC over a one-month modeling horizon were in telavancin strategy: RUB 516,286. The total costs of linezolid and vancomycin use were only 11% lower, calculated on the per patient basis. The evaluation of safety profiles of the strategies under analysis demonstrated that vancomycin strategy was associated with the highest number of AE. Telavancin strategy was more effective compared to other strategies under consideration: the clinical recovery rate was 86%, when the same value was somewhat lower in linezolid and vancomycin groups, 80.1% and 75%, respectively. Cost-effectiveness analysis makes it possible to conclude that telavancin use makes economic sense in terms of cost-effectiveness ratio. The results of the sensitivity analysis confirm the conclusions obtained in the main scenario.

Conclusions

1. Telavancin use as therapy for NP demonstrates high clinical effectiveness and one of the best safety profiles among other medical technologies for the treatment of this group of patients.
2. Telavancin use in therapy of NP makes economic sense in terms of cost-effectiveness ratio compared to vancomycin and linezolid.
3. According to the results of analysis of budget impact, for wide use estimated strategy requires additional investment to the extent of 13% when compared with the strategies of the use of vancomycin and linezolid.

Study limitations

This pharmacoeconomic analysis has the following peculiarities related to study limitation parameters. Firstly, safety and efficacy data used for effectiveness indicators and obtained in RCS differ from the conditions of actual practice and the conditions provided for in the model. Secondly, direct costs of aid for various nosologies were calculated with reference to the standards of care registered in the RF, while the description of the patient population and effectiveness indicators were taken from foreign studies.

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