№1 Том4 2016

Фармакоэкономика
теория и практика

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Pharmacoeconomics
theory and practice

№1 Volume4 2016

- МЕТОДОЛОГИЧЕСКИЕ ОСНОВЫ ФАРМАКОЭКОНОМИЧЕСКОГО МОДЕЛИРОВАНИЯ
- РЕЗУЛЬТАТЫ РОССИЙСКИХ ФАРМАКОЭКОНОМИЧЕСКИХ ИССЛЕДОВАНИЙ
- МАТЕРИАЛЫ X НАЦИОНАЛЬНОГО КОНГРЕССА С МЕЖДУНАРОДНЫМ УЧАСТИЕМ «РАЗВИТИЕ ФАРМАКОЭКОНОМИКИ И ФАРМАКОЭПИДЕМИОЛОГИИ В РОССИЙСКОЙ ФЕДЕРАЦИИ» 4-5 апреля 2016 г., г. Нижний Новгород

PHARMACOECONOMIC ANALYSIS OF COMBINATION OF MEDICINES DACLATASVIR AND ASUNAPREVIR IN TREATMENT OF CHRONIC HEPATITIS C IN THE RUSSIAN FEDERATION

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Abstract: *The goals of this study was: 1. to evaluate the superior regimen of antiviral drug treatment of chronic hepatitis C (daclatasvir + asunaprevir (a combination of the medicinal products) versus perginterferon alfa + ribavirin or peginterferon alfa + ribavirin + simeprevir or paritaprevir + ritonavir + ombitasvir + dasabuvir) in treatment-naive and treatment-experienced patients (HCV genotype 1b) without liver cirrhosis and with liver cirrhosis based on comparison of cost, effectiveness and safety; 2. To define, using «budget impact» analysis, economic outcomes of including daclatasvir + asunaprevir in current practice of HCV treatment This analysis was performed using two scenarios of the adjusted model "The MONARCH Cost-effectiveness Model". «Budget impact» analysis was conducted using adapted model* «ALLY: Daklinza® (Daclatasvir) Budget Impact Model». *The study demonstrated that the first study hypothesis was correct: the combination of the medicinal products for treatment of HCV-infection (HCV genotype 1) daclatasvir + asunaprevir was found to have advantages over the combinations peginterferon alfa + ribavirin, peginterferon alfa + ribavirin + simeprevir and dasabuvir, ombitasvir + paritaprevir + ritonavir in respect of the cost-effectiveness ratio. Furthermore, results of «budget impact» analysis confirmed the second study hypothesis – introduction of DCV + ASV in current practice of HCV treatment will lead to decreasing of complication treatment costs.*

Keywords: *chronic hepatitis c, genotype 1b, complications, liver cirrhosis, antiviral therapy, cost analysis, analysis of effectiveness, cost-effectiveness analysis.*

Chronic hepatitis C is a chronic liver disease lasting for more than 6 months, which is caused by hepatitis C virus (HCV) infection and HCV-induced hepatic injury and manifests by morphologic, necrotic, inflammatory and fibrosis changes in the hepatic tissue of varying severity [8].

More than twenty years have passed since the discovery of hepatitis C virus; however, no unified system of regular collection of statistical data regarding prevalence of the disease, distribution of patients according to fibrosis stage, presence of liver cirrhosis, incidence of HCV-related complications and other characteristics, which would allow to conduct a comprehensive analysis of distinctive features of the Russian population, has been developed so far in the Russian Federation. No unified data regarding AVT availability has been found as well.

At the same time activity related to compilation of the federal register of patients with viral hepatitis was commenced several years ago. According to available data, this register had been implemented in 39 subjects of the Russian Federation by the middle of 2015 [11].

The total number of HCV-infected patients living in the Russian Federation has been evaluated by experts as equal to 4-5 million people, while only 1.8 million HCV-infected patients were registered in 2012[3].

According to the data of the Federal Center for hygiene and epidemiology of the Federal Service for Surveillance on Consumer Rights Protection and Human Well-being, during 1999-2014 the incidence rate of chronic hepatitis C increased from 12.9 to 39.4 cases per 100,000 of population [11].

HCV-infection is unique in its own way, since in contrast to other viral infectious diseases, it is considered curable. The factors affecting treatment effectiveness and, as a result, probability of cure include the severity of the disease (such as the presence of liver cirrhosis), previous unsuccessful AVT-related experience, low adherence to therapy, ADR or HCV resistance to AVT regimen that is being used [2].

If left untreated or treated inadequately, chronic hepatitis C causes the development of complications such as liver fibrosis, liver cirrhosis or hepatocellular carcinoma.

The factors aggravating the course of the disease include age at the time of infection exceeding 40 years, male gender, non-caucasian race, alcohol abuse, obesity, iron metabolism impairment, and metabolic syndrome [8].

Furthermore, treatment effectiveness varies depending on HCV genotype the patient was infected with. In the Russian Federation the most prevalent HCV genotypes are 1b, 1a, 3a and 2 (the rest of genotypes are relatively rare).

In the Russian Federation approximately 0.1% of estimated number of patients with chronic hepatitis C (about 5,500 people) get access to AVT every year. [3].

In 2010, the economic burden of HCV-infection (acute and chronic hepatitis C) was evaluated at 48.47 billion rubles. About 35% of the economic burden is due to direct medical costs (medical care for patients with HCV-infection and its complications under outpatient and inpatient conditions). According to the modeling - based prognoses, in 2013-2030 the total sum of direct medical costs will comprise 127 billion rubles. It is important to note that the proportion of costs for chronic hepatitis C substantially exceeds that for acute hepatitis C [12].

Thus, the current situation requires relevant approach to issues regarding organization of medical care for HCV-infected patients (especially with chronic hepatitis C). This study was intended to prepare answers to a number of

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existing questions, specifically regarding pharmacoeconomic characteristics of different AVT regimens and to create evidence database, which could be use by the Russian healthcare authorities for decision-making.

The goals of this study was:

1. to evaluate the superior regimen of antiviral drug treatment of chronic hepatitis C (daclatasvir + asunaprevir (DCV + ASV) (a combination of the medicinal products) versus perginterferon alfa + ribavirin (PegIFN-α + RBV) or peginterferon alfa + ribavirin + simeprevir (PegIFN-α/RBV + SMV) or paritaprevir + ritonavir + ombitasvir + dasabuvir (Paritaprevir/r/Ombitasvir/+Dasabuvir)) in treatment-naive and treatment-experienced patients (HCV genotype 1b) without liver cirrhosis and with liver cirrhosis based on comparison of cost, effectiveness and safety;
2. to define using «budget impact» analysis economic outcomes of including DCV + ASV in current practice of HCV treatment.

The study hypothesizes were as follows:

1. the therapy regimen DCV + ASV is superior to PegIFN-α + RBV, PegIFN-α/RBV + SMV and Paritaprevir/r/Ombitasvir/+Dasabuvir regimens in terms of cost-effectiveness ratio;
2. introduction of DCV + ASV in current practice of HCV treatment will lead to decreasing of complication treatment costs.

Materials and methods

The global pharmacoeconomic model «The MONARCH Cost-effectiveness Model» developed by a group of investigators from Great Britain (Centre for Health Economics, Swansea University and Health Economics and Outcomes Research Ltd, South Wales) was obtained to reach the study purposes.

The model was prepared using Microsoft Office Excel software (Redmond, USA) and, according to the existing classification, belongs to so-called "Markov models". The model presumes simulation of development of chronic hepatitis C and its complications in a group of patients, given that the horizon of the model is equal to the duration of patients' life ("lifetime period"). The duration of one cycle was one year.

«ALLY: Daklinza® (Daclatasvir) Budget Impact Model» was based on the previously described «The MONARCH Cost-effectiveness Model» and considered economic burden of HCV for the short-term perspective (3 years).

Study scenarios:

1. for the group of AVT-naive patients with chronic hepatitis C (HCV genotype 1b);
2. for the group of AVT-experienced patients with chronic hepatitis C (HCV genotype 1b).

The determinate simulation technique was used (i.e. average values of the variables were used). Transition probabilities of moving from one health state to another were static.

The horizon of the model was equal to maximal possible duration of life of patients with chronic hepatitis C (80 years).

The discount rate of costs and effectiveness was 3.5%, which conforms to the existing methodology of carrying out pharmacoeconomic analysis.

The following antiviral therapy regimens used in patients with chronic hepatitis C (HCV genotype 1b) with cirrhosis and without cirrhosis were used as reference alternatives:

- DCV + ASV;
- PegIFN-α + RBV;
- PegIFN-α + RBV + SMV;
- Paritaprevir/r/ombitasvir /dasabuvir.

Characteristics of patients with chronic viral hepatitis C

A hypothetical group of averaged patients with chronic hepatitis C (HCV genotype 1b) was used as an analyzed group.

The number of patients in the group used for the first scenario was 2992 people. The information about the size of the group was obtained as a result of analysis of published data regarding the structure of chronic hepatitis C incidence in the Russian Federation for the period from 2011 to 2015 (Table 1).

The number of patients in the group used for the second scenario was 89 people. The information about the size of the group was obtained as a result of analysis of published data regarding the structure of chronic hepatitis C incidence in the Russian Federation for the period from 2011 till 2015 (Table 1).

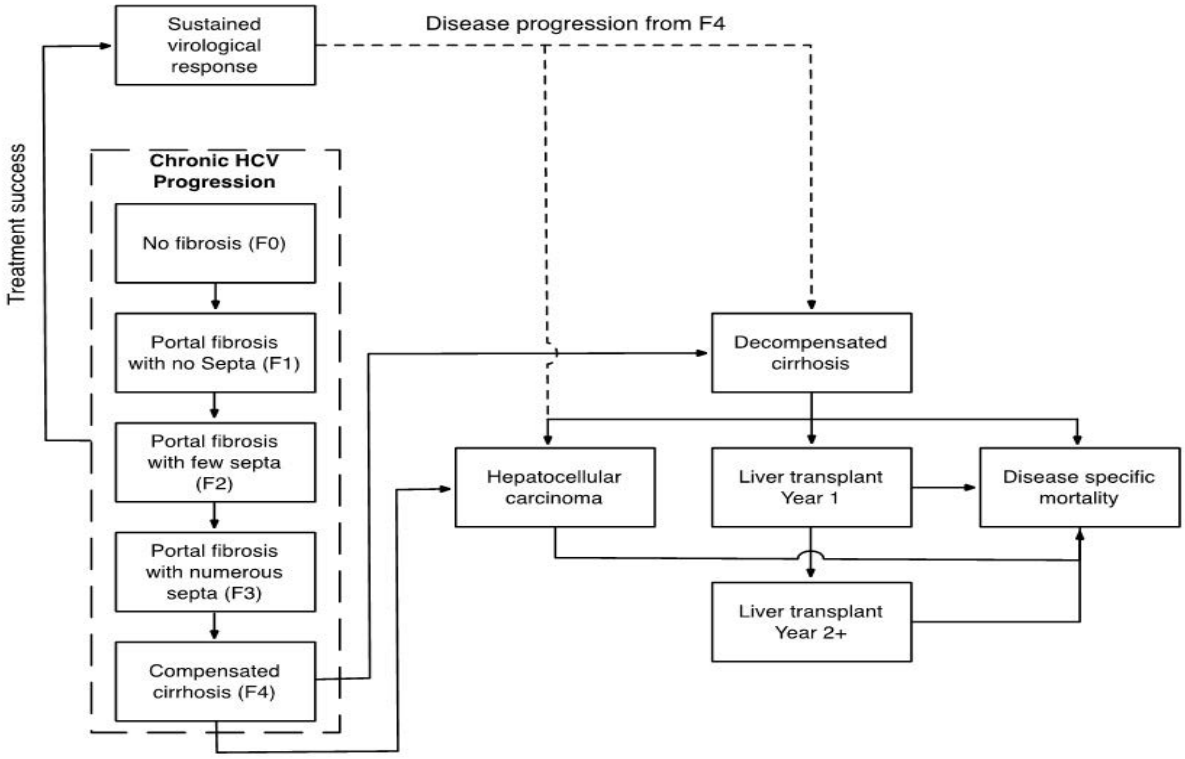


Figure 1. Flow chart of pharmacoeconomic model reflecting the order of events that occur during simulation modeling.

Table 1. Characteristics of the analyzed group of patients with chronic hepatitis C.

Parameter	Scenario 1	Scenario 2	Reference
Number of patients	2992	89	[9, 13]
Proportion of male patients, %	51.7		[10]
Average age, years	42.8		
Distribution according to fibrosis stage, %			
F0	38		
F1	24		
F2	17		
F3	9		
F4	12		

Analysis of effectiveness

The quality-adjusted life-year (QALY) parameter was used as a criterion for effectiveness of AVT regimens that were compared. Calculation of this parameter was performed using the model "The MONARCH Cost-effectiveness Model".

A proportion of patients who achieved sustained virologic response (SVR) - a parameter widely used in analyses of treatment effectiveness in clinical trials - was chosen as a surrogate end point. In order to determine the rates of SVR in patients receiving different AVT regimens, a search of available information and an analysis of the results of clinical studies were conducted.

Because of this work, we could not find any previous clinical study directly comparing all AVT regimens being analyzed. The analysis of published results of separate clinical studies and baseline characteristics of subjects in these studies showed that no data regarding achievement of SVR in a group of patients receiving the studied therapy regimens and having characteristics that completely coincide with those of the analyzed group of patients could be found. Besides, analysis of literature data demonstrated that the results of clinical studies had been presented for groups of patients with different characteristics.

However, the results of a study of indirect comparisons were found for DCV + ASV, SMV + PegIFN +RBV and PegIFN + RBV regimens.

Therefore, it was decided to divide the analysis of effectiveness (and, correspondingly, further pharmacoeconomic analysis) into two parts:

- Analysis of effectiveness: DCV + ASV, SMV + PegIFN +RBV and PegIFN + RBV;
- Analysis of effectiveness: DCV + ASV, Paritaprevir /r/Ombitasvir + Dasabuvir.

Analysis of efficacy: DCV + ASV, SMV + PegIFN +RBV and PegIFN + RBV;

The review of published literature revealed a study of indirect comparisons of effectiveness of regimens DCV + ASV, SMV + PegIFN +RBV and PegIFN + RBV, which used two methods CSL [7]:

1. Network meta-analysis (NMA);
2. Matching-adjusted indirect comparison (MAIC).

The individual characteristics of subjects in clinical studies of DCV + ASV and generalized characteristics of clinical studies participants receiving SMV + PegIFN +RBV and PegIFN + RBV found in published literature were used for the analysis conducted according to MAIC technique. The participants of the DCV + ASV clinical study were arranged (where possible) in accordance with inclusion and exclusion criteria for SMV + PegIFN +RBV and PegIFN + RBV regimens specified in publications. In order to level the existing differences in baseline characteristics of subjects in selected clinical studies the corresponding correction factors were used. These coefficients reduced the characteristics (age, BMI, sex, race, HCV blood plasma level, IL28B, HCV genotype, ALT level, bilirubin level, platelet count, cirrhosis stage) of the participants of the DCV + ASV clinical study to the generalized characteristics of the subjects of the SMV + PegIFN + RBV and PegIFN + RBV clinical studies in such a way that they coincided. After that the respective adjustment of the generalized data regarding DCV + ASV regimen effectiveness was performed. This reduction allowed comparing data on effectiveness of the specified AVT regimens which were "obtained" in groups of patients with similar generalized characteristics, i.e. this technique allowed to eliminate the existing heterogeneity between the patient groups from different clinical studies.

According to the results of the aforementioned study, DCV + ASV regimen was superior to SMV + PegIFN +RBV (treatment-experienced patients only) and PegIFN + RBV in respect of significantly higher SVR rate, which was demonstrated both in the network meta-analysis and in the matching-adjusted indirect comparison. Furthermore, this AVT regimen was significantly superior to the alternatives in respect of the number of cases of treatment-emergent anemia and rash.

Our pharmacoeconomic analysis was performed using the results obtained with MAIC technique (Table 2).

Table 2. Indirect comparison of the results of clinical studies (matching-adjusted indirect comparison)[7].

Patient group	Sustained virologic response (SVR), %			
	SMV+ PegIFN + RBV		PegIFN + RBV	
	DCV + ASV	SMV+ PegIFN + RBV	DCV + ASV	PegIFN + RBV
Treatment-naive	85.8	85.4	86.6	47.0
Treatment-experienced	96.2	85.9	93.8	36.2

Analysis of efficacy: DCV + ASV, Paritaprevir /r/Ombitasvir + Dasabuvir

Analysis of effectiveness was conducted using the technique of naive indirect comparison of efficacy. For the purposes of this analysis, published results of clinical studies involving the aforementioned AVT regimens were found. The data regarding the design, used effectiveness criteria, the number and characteristics of study subjects of these studies were then summarized and analyzed (Table 3).

The analysis allowed selecting several most comparable clinical studies that could be used for the most comprehensive indirect comparison of efficacy. It was assumed that all still existing heterogeneity between the groups of subjects in selected clinical studies could be disregarded.

The data regarding SVR achieved in patients receiving each of the analyzed therapy regimens are presented in Table 3.

Table 3. The results of a naive indirect comparison of the results of clinical studies.

Treatment regimen	DCV + ASV	Paritaprevir /r/ Ombitasvir + Dasabuvir + RBV-placebo	Paritaprevir /r/ Ombitasvir + Dasabuvir
The results are presented for HCV genotype	1b	1b	
The results are presented for fibrosis stage	F0-F3	F0-F3	
Duration of AVT, weeks	24	12	
SVR, %			
Treatment-naive	90,64	99,04	-
Treatment-experienced	79,43	-	100,00
Reference	[5, 6]	[4]	[1]

Analysis of costs

At the stage of cost analysis (consequently, in cost-effectiveness analysis and in «budget impact» analysis) only direct costs related to medical care for patients with chronic hepatitis C were taken into account (Fig. 2). The Federal Compulsory Medical Insurance Fund tariffs (valid in Moscow and Moscow Region) and medical care standards (or the data obtained using surveys of expert opinion, if no standards exist (Bogomolov P.O., Kuzmina O.S., Voronkova N.V., State Budgetary Healthcare Institution of Moscow Region «M.F. Vladimirskogo Moscow Regional Clinical Research Institute») were used as data sources.

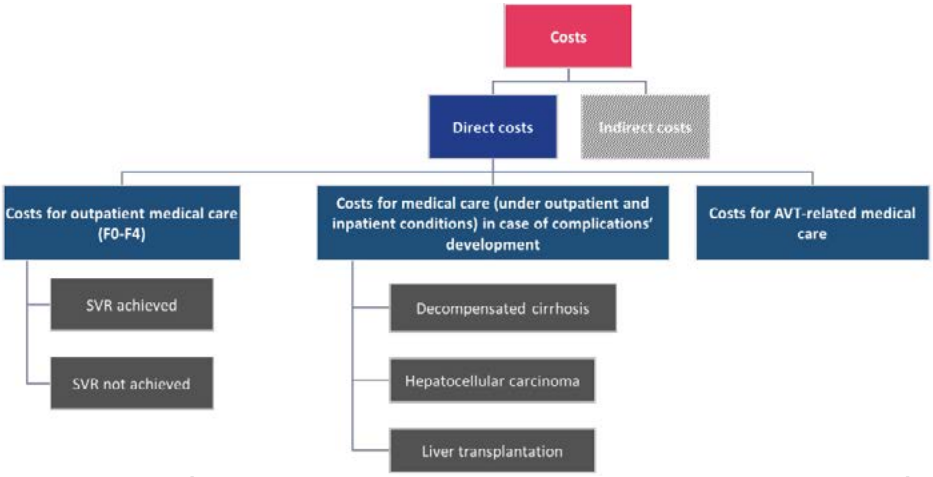


Figure 2. The structure of costs considered in this study.

The search for information allowed finding only two standards:

- The Decree of the Ministry of Health of the Russian Federation No.1584н dated December 28, 2012 "On approval of the standard of primary medical-sanitary aid in case of transplanted liver" (Registered in the Ministry of Justice of the Russian Federation No.27704 dated March 15, 2013);
- The Decree of the Ministry of Health of the Moscow region No.641 dated May 31, 2013 "On approval of regional standards of medical care" (the plan of management of patients with chronic hepatitis C (genotypes 1, 4) No.2.10.508.0).

The surveys of expert opinion were developed in such a way so it would be possible to collect the most comprehensive data regarding the structure of medical care costs for patients with relevant diseases under relevant conditions. Overall, the structure of the survey corresponded to the general structure of medical care standards, i.e. it allowed to collect the missing data regarding the results of physician-specialist examination, the results of laboratory tests and diagnostic investigations, and pharmacotherapy data.

The data on prices of analyzed medications were obtained according to the requirements of applicable parts of regulatory documents related to clinico-economic studies, the rules of price formation and purchasing of medicinal products included in the list of vital and the most important medicinal products:

- The Resolution of the Russian Government No.871 dated August 28, 2014 "On approval of the Rules of formation of lists of medicinal products for medical use and the minimum choice of medicinal products required for medical care";
- The Federal law No.61 dated April 12, 2010 (revised version dated July 13, 2015) "On circulation of medicinal products" (with amendments and updates effective July 24, 2015);
- The Federal law No.44 dated April 05, 2013 (revised version dated July 13, 2015) "On contractual system in the field of purchases of good, works, services for state and municipal needs" (with amendments and updates effective August 13, 2015);

The prices of medicinal products that were components of the analyzed regimens were obtained (in case there was a maximum allowable selling price of a medicinal product registered in accordance with the established procedure) from the State Register of maximum selling prices of medicinal products including VAT. In case there was no maximum allowable selling price of a medicinal product registered in accordance with the established procedure, the median price of reproduced medicinal product during actual purchases was used (according to the data of electronic auctions for medicinal product purchases for state and municipal needs) (source: Headway Company) (Table 4).

The prices of other registered medicinal products (included in the structure of direct medical care costs but not used for comparison in this study) were obtained from the web-portal http://www.pharmindex.ru/. Median wholesale price or (if not available) median retail price was used as the price for calculations.

Table 4. The data on prices of the medicinal products that are components of the regimens analyzed.

INN	PegIFN-α-2a	PegIFN-α-2b	SMV	Paritaprevir /r/ ombitasvir / dasabuvir	RBV	DCV	ASV
Strength	180 μg/ 0.5 mL No.1	120 μg/ 0.7 mL No.1	150 mg No. 28	No. 28	200 mg No.120	60 mg No. 30	100 mg No. 56
The price of one package (including VAT)	9 607 ₽	9 491 ₽	453 794 ₽	317 786 ₽	2 101 ₽	116 783 ₽	11 733 ₽
Reference	[14]	[14]	[15]	[15]	[14]	-	-

[1] The presumed tender prices of daclatasvir and asunaprevir are specified based on the prices indicated in the manufacturer's list of prices.

[2.] The average tender price of effective in the Russian Federation for the period from January 01, 2015 to November 03, 2015 (http://www.zakupki.gov.ru/) was calculated without taking into account the tenders conducted in the Moscow Region, where special tariffs are used for management of patients with chronic hepatitis (approved by the Committee for development of the Moscow Regional Compulsory Medical Insurance program dated December 25, 2013 for day hospitals in municipal healthcare facilities and the Moscow Regional Center for Hepatology of the State Budgetary Healthcare Institution of the Moscow Regional Research Clinical Institute named after M.F. Vladimirky").

[3.] For the rest of the products average tender prices used in the Russian Federation for the period from 1st January 2015 to 30th September 2015 are indicated (according to the data provided at http://www.zakupki.gov.ru/). Among PEGylated interferons, the medicinal product Algeron® was chosen for calculation of the cost of triple regimen as this product had shown the least tender price throughout the course of treatment within the selected period. Average tender price of ribavirin was calculated taking into account all its trade names.

[4.] The maximum allowable selling prices that were registered in accordance with established procedure conformed to the records of the State Register of medicinal products dated November 02, 2015.

The results - cost-effectiveness analysis scenario 1: DCV + ASV, SMV + PegIFN +RBV and PegIFN + RBV;

The conducted analysis showed that DCV + ASV regimen was associated with less AVT-related costs (monitoring costs) as compared with both alternative regimens, as well as with less costs for AVT-related pharmacotherapy as compared to SMV + PegIFN-α + RBV regimen (Table 5).

Moreover, the analysis demonstrated that the total costs for medical care related to the disease progression in patients receiving DCV + ASV was significantly lower as compared with SMV + PegIFN-α + RBV and PegIFN-α + RBV therapy regimens.

Overall, total costs per 1 patient comprised 906,365 rubles and 1,702,054 rubles for DCV + ASV and SMV + PegIFN-α + RBV regimens, respectively, and 902,682 rubles and 866,806 rubles for DCV + ASV and PegIFN-α + RBV regimens, respectively.

The results of analysis of effectiveness showed that use of DCV + ASV was associated with higher SVR, LY and QALY parameters.

The calculation of the incremental cost-effectiveness ratio showed that among the two regimens DCV + ASV and SMV + PegIFN-α + RBV the former was strictly superior, and that the coefficient for QALY calculated for the two regimens DCV + ASV and PegIFN-α + RBV comprised 23,556 rubles (Table (6), which is by 1.24 million rubles lower (the value of "willingness to pay threshold" calculated according to the WHO).

Table 6. The results of cost-effectiveness analysis: treatment-naive patients with chronic hepatitis C (discount rate=3.5%).

	SMV + PegIFN-α + RBV		PegIFN-α + RBV	
	DCV + ASV	SMV + PegIFN-α + RBV	DCV + ASV	PegIFN-α + RBV
Total costs per 1 patient, rubles	906 365	1 702 054	902 682	866 806
Efficacy				
SVR, %	85,80	85,40	86,60	47,00
LY	20,64	20,63	20,65	19,87
QALY	15,79	15,77	15,82	14,30
The number of patients with chronic hepatitis C	2992	2992	2992	2992
The number of cases in which SVR was achieved	2567	2555	2591	1406
CER (QALY)	57 401	107 930	57 060	60 616
ICER (LY)	Superior regimen DCV + ASV		46 039	
ICER (QALY)	Superior regimen DCV + ASV		23 556	

The results - cost-effectiveness analysis scenario 1: DCV + ASV, Paritaprevir /r/Ombitasvir + Dasabuvir

The conducted analysis demonstrated that use of ABT-450/r/Ombitasvir + Dasabuvir regimen was associated with less AVT-related monitoring costs as compared with the alternative regimen. However, the AVT-related pharmacotherapy costs were lower when DCV + ASV regimen was used (Table 7).

Moreover, the analysis demonstrated that the total costs for medical care related to the disease progression in patients receiving ABT-450/r/Ombitasvir + Dasabuvir was significantly lower as compared with DCV + ASV therapy regimen.

Table5. The results of cost analysis: treatment-naive patients with chronic hepatitis C (discount rate=3.5%).

	SMV + PegIFN-α + RBV		PegIFN-α + RBV	
	DCV + ASV	SMV + PegIFN-α + RBV	DCV + ASV	PegIFN-α + RBV
The costs for patient care during AVT (laboratory tests and medical services), rubles	177 397 415	177 397 415	177 397 415	349 231 485
AVT costs (only medications), rubles	2 167 309 056	4 542 502 272	2 167 309 056	1 342 665 984
Total AVT-related costs, rubles	2 344 706 471	4 719 899 687	2 344 706 471	1 691 897 469
Costs of medical care for a patient with chronic hepatitis C (patient care, treatment of complications), rubles	367 136 475	372 646 250	356 116 925	901 584 664
Total costs, rubles	2 711 842 946	5 092 545 938	2 700 823 396	2 593 482 133
The number of patients with chronic hepatitis C	2992	2992	2992	2992
Total costs per 1 patient with chronic hepatitis C, rubles	906 365	1 702 054	902 682	866 806
Total costs per 1 SVR case, rubles	1 056 369	1 993 038	1 042 358	1 844 267
Total costs of AVT per 1 SVR case, rubles	913 355	1 847 197	904 918	1 203 136

Overall, total costs per 1 patient comprised 882,425 rubles and 1,045,759 rubles for DCV + ASV and ABT-450/r/Ombitasvir + Dasabuvir regimens, respectively.

The results of analysis of effectiveness showed that use of Paritaprevir /r/Ombitasvir + Dasabuvir was associated with higher SVR, LY and QALY parameters, while the cost-effectiveness ratio was lower when DCV + ASV regimen was used (Table 8).

The calculation of the incremental cost-effectiveness ratio showed that the coefficient for QALY calculated for the regimens DCV + ASV and Paritaprevir /r/Ombitasvir + Dasabuvir comprised 510,339 rubles (Table 8).

The results - cost-effectiveness analysis scenario 2: DCV + ASV, SMV + PegIFN +RBV and PegIFN + RBV

The conducted analysis showed that DCV + ASV regimen was associated with less AVT-related costs (monitoring costs) as compared with both alternative regimens, as well as with less costs for AVT-related pharmacotherapy as compared to SMV + PegIFN-α + RBV regimen (Table 9).

Moreover, the analysis demonstrated that the total costs for medical care related to the disease progression in patients receiving DCV + ASV was significantly lower as compared with SMV + PegIFN-α + RBV and PegIFN-α + RBV therapy regimens.

Table 7. The results of analysis of costs: antiviral treatment-naive patients with chronic hepatitis C (discount rate=3.5%).

	DCV + ASV	Paritaprevir/r/ Ombitasvir + Dasabuvir
Costs of patient management during AVT, rubles	177 397 415	91 167 978
Total AVT costs (medications), rubles	2 167 309 056	2 852 429 184
Total AVT-related costs, rubles	2 344 706 471	2 943 597 162
Costs for medical care for a patient with chronic hepatitis C (patient care, treatment of complications), rubles	295 509 398	185 313 895
Total costs, rubles	2 640 215 870	3 128 911 058
The number of patients with chronic hepatitis C	2992	2992
Total costs per 1 patient with chronic hepatitis C, rubles	882 425	1 045 759
Total costs per 1 SVR case, rubles	969 698	1 056 322
Total costs of AVT per 1 SVR case, rubles	861 163	993 760

Table 8. The results of cost-effectiveness analysis: antiviral treatment-naive patients with chronic hepatitis C (discount rate=3.5%).

	DCV + ASV	Paritaprevir /r/Ombitasvir + Dasabuvir
Total costs per 1 patient, rubles	882 425	1 045 759
Efficacy		
SVR, %	90,64	99,04
LY	20,74	20,90
QALY	15,99	16,31
The number of patients with chronic hepatitis C	2992	2992
The number of cases in which SVR was achieved	2723	2962
CER (QALY)	55 186	64 118
ICER (LY)	1 037 533	
ICER (QALY)	510 339	

Overall, total costs per 1 patient comprised 858,486 rubles and 1,699,752 rubles for DCV + ASV and SMV + PegIFN-α + RBV regimens, respectively, and 869,535 rubles and 916,526 rubles for DCV + ASV and PegIFN-α + RBV regimens, respectively.

The results of analysis of effectiveness showed that use of DCV + ASV was associated with higher SVR, LY and QALY parameters.

The calculation of the incremental cost-effectiveness ratio showed that in the pair of regimens DCV + ASV and SMV + PegIFN-α + RBV, as well as in the pair DCV + ASV and PegIFN-α + RBV the first regimen was strictly superior (Table 10).

Table 9. The results of analysis of costs: treatment-experienced patients with chronic hepatitis C (discount rate=3.5%).

	SIM + pIFN-α + RBV		pIFN-α + RBV	
	DCV + ASV	SIM + pIFN-α + RBV	DCV + ASV	pIFN-α + RBV
Costs of patient management during AVT, rubles	5 276 862	5 276 862	5 276 862	10 388 236
Total AVT costs (medications), rubles	64 468 752	135 121 224	64 468 752	39 938 928
Total AVT-related costs, rubles	69 745 614	140 398 086	69 745 614	50 327 164
Costs of medical care for a patient with chronic hepatitis C (patient's care, treatment of complications), rubles	6 659 601	10 879 864	7 642 963	31 243 658
Total costs, rubles	76 405 215	151 277 950	77 388 577	81 570 822
The number of patients with chronic hepatitis C	89	89	89	89
Total costs per 1 patient with chronic hepatitis C, rubles	858 486	1 699 752	869 535	916 526
Total costs per 1 SVR case, rubles	892 397	1 978 757	927 009	2 531 840
Total costs of AVT per 1 SVR case, rubles	814 614	1 836 445	835 457	1 562 082

Table 10. The results of cost-effectiveness analysis: treatment-experienced patients with chronic hepatitis C (discount rate=3.5%).

	SMV + PegIFN-α + RBV		PegIFN-α + RBV	
	DCV + ASV	SMV + PegIFN-α + RBV	DCV + ASV	PegIFN-α + RBV
Total costs per 1 patient, rubles	858 486	1 699 752	869 535	916 526
Efficacy				
SVR, %	96,20	85,90	93,80	36,20
LY	20,84	20,64	20,80	19,60
QALY	16,19	15,79	16,09	13,89
The number of patients with chronic hepatitis C	89	89	89	89
The number of cases in which SVR was achieved	86	76	83	32
CER (QALY)	53 026	107 647	54 042	65 985
ICER (LY)	Superior regimen DCV + ASV		Superior regimen DCV + ASV	
ICER (QALY)	Superior regimen DCV + ASV		Superior regimen DCV + ASV	

The results - cost-effectiveness analysis scenario 2: DCV + ASV, Paritaprevir /r/Ombitasvir + Dasabuvir

The conducted analysis demonstrated that use of ABT-450/r/Ombitasvir + Dasabuvir regimen was associated with less AVT-related monitoring costs as compared with the alternative regimen. However, the AVT-related pharmacotherapy costs were lower when DCV + ASV regimen was used (Table 11).

Moreover, the analysis demonstrated that the total costs for medical care related to the disease progression in patients receiving **Paritaprevir** /r/Ombitasvir + Dasabuvir was significantly lower as compared with DCV + ASV therapy regimen.

Overall, total costs per 1 patient comprised 931,096 rubles and 1,041,155 rubles for DCV + ASV and Paritaprevir/r/Ombitasvir + Dasabuvir regimens, respectively.

The results of analysis of effectiveness showed that use of Paritaprevir/r/Ombitasvir + Dasabuvir was associated with higher SVR, LY and QALY parameters, while the cost-effectiveness ratio was lower when DCV + ASV regimen was used (Table 12).

The calculation of the incremental cost-effectiveness ratio showed that the coefficient for QALY calculated for the regimens DCV + ASV and Paritaprevir/r/Ombitasvir + Dasabuvir comprised 145,263 rubles (Table 12).

Table 11. The results of analysis of costs: treatment-experienced patients with chronic hepatitis C (discount rate=3.5%).

	DCV + ASV	Paritaprevir /r/Ombitasvir + Dasabuvir
Costs of patient management during AVT, rubles	5 276 862	2 711 882
Total AVT costs (medications), rubles	64 468 752	84 848 328
Total AVT-related costs, rubles	69 745 614	87 560 210
Costs for medical care for a patient with chronic hepatitis C (patient's care, treatment of complications), rubles	13 121 939	5 102 611
Total costs, rubles	82 867 553	92 662 821
The number of patients with chronic hepatitis C	89	89
Total costs per 1 patient with chronic hepatitis C, rubles	931 096	1 041 155
Total costs per 1 SVR case, rubles	1 164 452	1 041 155
Total costs of AVT per 1 SVR case, rubles	980 063	983 823

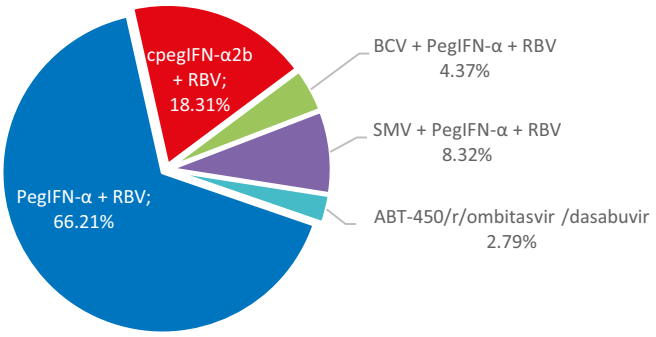
Table 12. The results of cost-effectiveness analysis: treatment-experienced patients with chronic hepatitis C (discount rate=3.5%).

	DCV + ASV	Paritaprevir /r/ Ombitasvir + Dasabuvir
Total costs per 1 patient, rubles	931 096	1 041 155
Efficacy		
SVR, %	79,43	100,00
LY	20,55	20,92
QALY	15,59	16,35
The number of patients with chronic hepatitis C	89	89
The number of cases in which SVR was achieved	70	89
CER (QALY)	59 724	63 679
ICER (LY)	302 078	
ICER (QALY)	145 263	

Results – «budget impact» analysis

Conducted during current study analysis of state and municipal purchases medicines included in antiviral treatment for the period 01.01.15-03.11.15 demonstrated that the major part of the market belongs to PegIFN-α + RBV (66,21%) (pic. 3).

In keeping with obtained market shares, it was assumed that market shares of DCV + ASV after including in practice of treatment of HCV patients with F0-F4 would be 7%, 10% and 13% in 2016, 2017 and 2018, respectively.



Picture 3. Market shares based on the analysis of state and municipal purchases.

Results of «budget impact» analysis demonstrated that within the short-term perspective (3 years) 9009 patients (HCV genotype 1b) with F0-F4 would be treated with antiretroviral schemes. At this, costs of initial antiviral treatment would increase up on 8609 rub. per 1 patient, and would lead to decrease of complications treatment costs (associated with the treated patients) on 5571925 rub.

Conclusions

Thus, cost-effectiveness analysis conducted using two scenarios of the adjusted model "The MONARCH Cost-effectiveness Model" demonstrated that the first study hypothesis was confirmed since the combination of the medicinal products for treatment of HCV-infection (HCV genotype 1) daclatasvir + asunaprevir was found to be superior to the combinations peginterferon alfa + ribavirin, peginterferon alfa + ribavirin + simeprevir and dasabuvir, ombitasvir + paritaprevir + ritonavir in terms of cost/effectiveness ratio:

The first scenario (for the group of AVT-naive patients) indicated that the combination daclatasvir + asunaprevir was superior in respect of cost-effectiveness analysis as compared with the combination of peginterferon alfa + ribavirin + simeprevir and was characterized by better cost-effectiveness ratio as compared with the regimens peginterferon alfa + ribavirion and dasabuvir, ombitasvir + paritaprevir + ritonavir;

The second scenario (for the group of AVT-experienced patients) indicated that the combination daclatasvir + asunaprevir was superior in respect of cost-effectiveness analysis as compared with the combination of peginterferon alfa + ribavirin and peginterferon alfa + ribavirin+ simeprevir; and was characterized by better cost-effectiveness ratio as compared with the regimens dasabuvir, ombitasvir + paritaprevir + ritonavir.

Furthermore, results of «budget impact» analysis obtained via «ALLY: Daklinza® (Daclatasvir) Budget Impact Model» confirmed the second study hypothesis – introduction of DCV + ASV in current practice of HCV treatment will lead to decreasing of complication treatment costs. Significantly, that the «ALLY» model considers only direct costs appeared in the three-year period, but the most severe complications develop in longer-term perspective, therefore the avoided costs of complications treatment could increase even more.

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