British Journal of Pharmaceutical Research
13(2): 1-9, 2016, Article no.BJPR.27144
ISSN: 2231-2919, NLM ID: 101631759

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Pharmacoeconomic Analysis of Direct Activity Antiviral Drugs Used for Treatment of Genotype 1 Chronic Hepatitis C

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Authors' contributions

This work was carried out in collaboration between all authors. Author NZM designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors AGS and OMK managed the analyses of the study and the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJPR/2016/27144
Editor(s):
(1) Mohamed Fathy, Assiut University, Assiut, Egypt.
Reviewers:
(1) Anonymous, Belgrade University, Serbia.
(2) Muhammad Akram, The University of Poonch, Rawalakot, Azad Jammu and Kashmir, Pakistan.
(3) Ozcan Deveci, University of Dicle, Diyarbakır, Turkey.
(4) Vassilios A. Sevastianos, "Evangelismos" General Hospital, Greece.
Complete Peer review History: http://www.sciencedomain.org/review-history/16215

Original Research Article

Received 20th May 2016
Accepted 7th September 2016
Published 19th September 2016

ABSTRACT

Aims: Hepatitis C is one of the most important global health care problems. The goal of this study was to perform a pharmacoeconomic analysis of therapeutic schemes used in treatment of patients with genotype 1 chronic HCV by using direct-acting antiviral agents in combination with pegylated interferons and ribavirin.
Study Design: In the current study comparison of therapeutic schemes used in treatment of patients with genotype 1 chronic HCV by using direct-acting antiviral agents in combination with pegylated interferons and ribavirin was made.
Place and Duration of Study: Moscow Institute of Physics and Technology (State University), Department of Biological and Medical Physics, Laboratory of government programs and development projects in life sciences (April 2015 - November 2015).
Methodology: In the current study Markov decision process model was built in order to assess long-term costs and efficacy of preparations under study. Comparison of therapeutic schemes for

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chronic HCV infection treatment was performed with the use of cost-effectiveness and cost-utility analysis. In costs-effectiveness analysis, therapeutic schemes for CHC treatment that include telaprevir, boceprevir and simeprevir, life years gained (LYG) and quality adjusted life years (QALY) served as a criterion of benefit in costs-effectiveness and cost-utility analysis respectively.

Results: Pharmacoeconomic analysis of treatment of chronic hepatitis C viral infection showed that the best combination of costs and effectiveness was observed in combined treatment with the use of pegylated interferon, ribavirin and boceprevir in treatment-naïve patients as well as patients with unsuccessful treatment experience.

Conclusion: Our results showed that combined therapy with the use of boceprevir is the most pharmacoeconomically justified in comparison with telaprevir and simeprevir-based treatment.

Keywords: Hepatitis C; boceprevir; telaprevir; simeprevir.

1. INTRODUCTION

Hepatitis C is one of the most important global health care problems. According to the World Health Organization report between 130–150 million people globally have chronic hepatitis C infection [1]. Approximately 700 000 people die each year from hepatitis C-related liver diseases [2]. The most frequent complications of chronic hepatitis C (CHC) are liver cirrhosis and hepatocellular carcinoma that cause loss of capacity for work and premature death. There is a high level of hepatitis C virus (HCV) infection in Russian Federation, and the morbidity is still increasing. According to Russian Federal Service for Surveillance on Consumer Rights Protection and Human Well-being (Rospotrebnadzor), 57 197 incidences of HCV infection (39.94 cases per 100 000 people) were registered in Russian Federation in 2014.

As compared with 2013, annual morbidity growth was equal to 1.7% [3]. Importantly, genotype 1 hepatitis C virus is a dominant form (80%) in Russian Federation, and it is highly resistant to therapy [4]. Survey of hepatitis C impact on Russian economy revealed that the disease-related losses exceeded 48 billion rubles or 0.11% of Gross Domestic Product (GDP) in 2010. Additionally, the greatest part of medical costs was associated with CHC complications [5]. Thus, hepatitis C is socially important disease and its dissemination leads to serous economic losses.

Timely diagnostics and treatment of hepatitis C allows to prevent serious complications and even to achieve complete liver regeneration. Until recently, a combined therapy with the use of interferon or pegylated interferon (PI) and ribavirin (R) during 24 or 48 weeks was recognized as a “golden standard” in hepatitis C treatment. Principally new class of direct-acting antiviral agents (DAA) that represent inhibitors of NS3/4A protease was introduced into clinical practice in 2011. Usage of such preparations provides significant increase in therapeutic efficacy and safety. However, this causes increase in costs of the drug-based therapeutics due to high prices of new preparations. Therefore, pharmacoeconomic efficacy in DAA usage becomes the most important issue.

To date, telaprevir, boceprevir and simeprevir are registered in Russian Federation as DAA. These drugs are recommended for usage in combination with PI and R in triple therapy of genotype 1 HCV-carrying patients, both treatment-naïve and unsuccessfully treated with the use of PI or R. According to European Association for Study of Liver Recommendations on Treatment of Hepatitis C 2015 triple combination of PI, R and either telaprevir or boceprevir, remain acceptable for selected patients likely to respond to these regimens until new DAAs become available and affordable [6].

Development of sustainable viral response (SVR), i.e. the absence of hepatitis C viral RNA for 24 weeks after treatment completion serves as a criterion of treatment efficacy. Additionally, rapid virological response (RVR) and early viral response (EVR) represent intermediate criteria to assess treatment efficacy and to determine duration and type of therapeutic scheme.

The goal of this study was to perform comparative pharmacoeconomic analysis of therapeutic schemes used in treatment of patients with genotype 1 chronic HCV by using DAAs (boceprevir, simeprevir and telaprevir) in combination with pegylated interferons and ribavirin.

2. MATERIALS AND METHODS

Initially, a systematic review was performed to evaluate efficacy and safety of preparations used to treat patients with genotype 1 HCV, both treatment-naive and unsuccessfully treated with PI and R. For this purpose, Clinical trials.gov and Medline databases were used. Results of completed efficacy studies were selected, in which the preparations were used in doses recommended by special instructions for a certain cohort of patients. Patients with combined HIV/HCV infection were not taken into consideration. The results obtained are shown in Table 1.

2.1 Mathematical Model of the Disease

Markov decision process model was further built in order to assess long-term costs and efficacy of preparations under study. The Markov model represents a mathematical model that is given by a final set of discrete states named Markov states, and by probabilities of transitioning from one state to another in a given time interval termed Markov cycle. Costs and utilities during one cycle represent parameters under study. According to this model, a patient exist in one of the discrete states during a cycle. Then, at the end of one Markov cycle, transition from one state to another is possible with a probability determined by data of clinical studies.

Based on scientific literature review, in particular, publications concerning naturally occurring hepatitis C, the disease model has been developed with 9 states in total (Fig. 1). Here, Fig. 1 does not depict the adsorbing state «Death». Death probability was calculated as a sum of probabilities of death resulted from both liver diseases and all other reasons. Death probability associated with reasons other than liver diseases was calculated on the basis of Tables of Mortality in Russian Federation [17].

Table 1. Clinical studies on evaluation of a preparation efficacy in treatment of genotype 1 CHC patients. PI – pegylated interferon, R – ribavirin

DAA	Clinical trial	Group of patients	Therapeutic scheme
Telaprevir	ADVANCE [7]	Treatment-naive	1) Telaprevir + PI + R for 12 weeks, then PI + R for 12 weeks 2) Telaprevir + PI + R for 12 weeks, then PI + R for 36 weeks
	REALIZE [8]	Previously unsuccessfully treated with PI and PI+R	Telaprevir + PI + R for 12 weeks, then PI + R for 36 weeks
Boceprevir	SPRINT-2* [9]	Treatment-naive	1) PI + R for 4 weeks, then boceprevir + PI + R for 24 weeks 2) PI + R for 4 weeks, then boceprevir + PI + R for 24 weeks, then PI + R 12 weeks
	RESPOND-2* [10]	Previously treated, partly responded or relapsed after previous treatment PI+R	1) PI + P for 4 weeks, then boceprevir + PI + R for 32 weeks 2) PI + Pfor 4 weeks, then boceprevir + PI + R for 32 weeks, then P I+ R for 12 weeks
	P05685* [11]		
	PROVIDE [12]	Previously treated with no response	PI + R for 4 weeks, then boceprevir + PI + R for 44 weeks
Simeprevir	QUEST-1 [13] QUEST-2 [14]	Treatment-naive	Simeprevir + PI + R for 12 weeks, then PI + R for 12 weeks
	PROMISE [15]	Previously unsuccessfully treated	Simeprevir + PI + R for 12 weeks, then PI + R for 24 weeks

** The therapeutic schemes in clinical studies do not consistent with schemes presented in the boceprevir user's protocol. Company producing the preparation performed retrospective analysis of data regarding the preparation efficacy in accordance with the dosage regimen stated in the preparation protocol [16].*

1) In case of RVR and EVR;

2) In absence of RVR and EVR

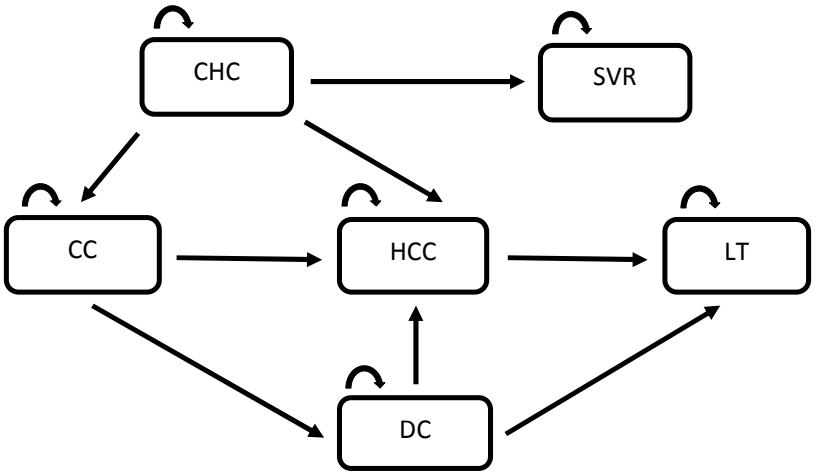

Fig. 1. Markov model of hepatitis C

Death probabilities associated with liver diseases for all states, except SVR, were obtained from literature sources [18,19]. Death probability after liver transplantation (LT) depended on time elapsed after transplantation. Other probabilities were obtained from analysis of literature sources [20-25]. In the model described here, probability of SVR development for different therapeutic schemes is given taking into account results of clinical studies shown in Table 1. Time horizon varies from 1 to 10 years, the cycle length is 1 year. Discount coefficient is equal to 3%.

3. RESULTS AND DISCUSSION

3.1 Cost Analysis

Further, calculation of costs of the presence in each state of Markov model was performed. Costs of drug therapy (DT), medical services (MS) and costs attributable to adverse events (AE) were calculated. To calculate costs of DT and AEC, we used prices fixed in Federal Register of Price Limits for producers of medicinal preparations, included into list of crucial, pivotal medicinal preparations stated on April 25, 2015 [26] and in Pharmacies and Medical Services Directory in Moscow. In order to calculate MS costs, a Patient Price List of Clinical Center at I.M. Sechenov First Moscow State Medical University, accepted on December 1, 2014 was used. Costs of medical services for all groups of patients are consistent with standard protocols for outpatient treatment. Total costs for each state of the model are presented in Table 2.

Table 2. Costs of Markov model states

State	Costs (US dollar)
CHC	*
SVR	0
CC	2 467
DC	4 593
HCC	2 474
LT	13 667
Death	0

** depends on therapeutic scheme*

Calculation of therapeutic costs was performed according to corresponding standards and tariffs for the following states: «Chronic hepatitis C» [27], «Compensated cirrhosis» and «Decompensated cirrhosis» [28], «Hepatocellular carcinoma» [29], «Liver transplantation» [30]. The «Sustainable virus response» state in the model corresponds to complete recovery. Costs of a given state and a probability of transit onto other states were accepted to be equal to zero.

Calculation of costs attributable to adverse events was performed in accordance with their frequencies in usage of different therapeutic schemes. Costs attributable to adverse events were calculated for all adverse events that can be managed by other medications. Thus, we calculated costs of anemia, neutropenia, thrombocytopenia, depression, nausea, diarrhea, pruritus, rash, flu-like syndrome, headache and insomnia managing. Hematological effects (anemia, neutropenia and thrombocytopenia) were the most often. In clinical studies anemia correction was made with decrease in antiviral preparations dosage or erythropoietin administration or combination of both measures

[7,8,9,10,11,13,14,15] to assess efficacy and safety of DAA in triple therapy. However, decreasing antiviral preparations dosage reduced SVR probability [31]. Taking this circumstance into account and to make calculations easier a decision to administrate erythropoietin, eltrombopagand and filgrastim to all patients with anemia, thrombocytopenia and neutropenia respectively was made [32].

Costs of «Chronic hepatitis C» group varied depending on a therapeutic scheme and a patient cohort (Fig. 2). For treatment-naïve patients, a triple therapy scheme with the use of boceprevir was the most cost-effective. Triple therapy scheme with the use of telaprevir was the least expensive for patients treated before.

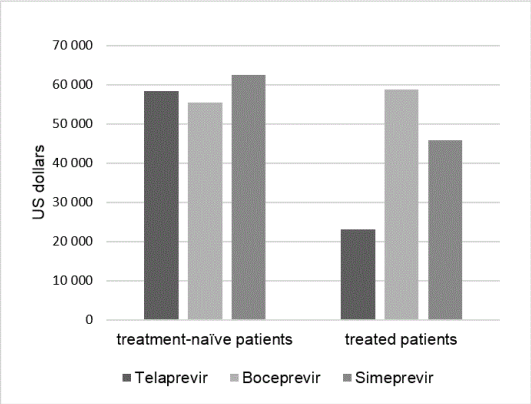

Fig. 2. Annual costs for patients with CHC per capita depending on DAA used in combined scheme of HCV treatment

3.2 Comparative Analysis of Therapeutic Schemes

Comparison of therapeutic schemes for chronic HCV infection treatment that include telaprevir, boceprevir and simeprevir was performed with the use of cost-effectiveness and cost-utility analysis. In costs-effectiveness analysis, therapeutic schemes for CHC treatment that include telaprevir, boceprevir and simeprevir, life years gained (LYG) and quality adjusted life years (QALY) served as a criterion of benefit in costs-effectiveness and cost-utility analysis respectively. To calculate QALY, utilities relevant to each state, obtained from literature sources were used [16].

Long-term results regarding costs, LYGs and QALYs were obtained by simulation of the 1000 patients with chronic hepatitis C virus infection cohort. Modeling was performed separately for 2 subpopulations of patients, treatment-naïve and previously unsuccessfully treated. Patients' characteristics and state distribution in Markov model at the beginning of the simulation corresponded to epidemiologic data on hepatitis C dissemination in Russian Federation [3]. According to these data, the average age of patients with hepatitis C equals to 40 years. Liver cirrhosis prevalence among this group of patients was about 15%. So, it was admitted that 85% of patients are in «Chronic hepatitis C» state, while 15% of patients are in «Compensated cirrhosis» at the starting point.

Markov model simulation resulted in cumulative costs, cumulative life years gained (LYG), cumulative quality adjusted life years (QALY) per a cohort of 1,000 patients with chronic hepatitis C. Then, these cumulative values were counted for one patient.

3.3 Cost-effectiveness Analysis

Results of primary cost-efficacy analysis are presented in Table 3.

Table 3 shows that treatment with boceprevir for 1, 5 and 10 years is less expensive and more effective in comparison with alternative schemes for previously treated patients with hepatitis C virus infection. Thus, the boceprevir-based therapy is a strongly dominating technology for this group of patients.

In the group of treatment-naïve patients, the same values of life years gained equal to 2.0, 5.5 and 9.1 are observed during 1, 5 and 10 years of treatment, respectively, with telaprevir and simeprevir. Thus, the simeprevir-based treatment is excluded from analysis due to its higher costs comparing with telaprevir-based technology.

Further, the cost-effectiveness coefficient (CER), and incremental cost-effectiveness coefficient (ICER) (Table 4) were calculated. Cost-effectiveness coefficient was calculated as a ratio of cost difference and effectiveness difference (life years gained) for therapeutic schemes studied. ICER was calculated according to the following formula:

ICER = Cost2 – Cost1/Ef2 – Ef1, where Cost is cost of CHC treatment, Ef is effectiveness.

Table 3. Results of pharmacoeconomic analysis of DAAs used in combined treatment (with pegylated interferon and ribavirin) of CHC infection

Time period	Group	Treatment-naïve patients		Treated patients	
	DAA	Costs (US dollar)	Life years gained (LYG)	Costs (US dollar)	Life years gained (LYG)
1 year	Telaprevir	8 951	2.0	11 363	2.0
	Boceprevir	12 422	3.9	8 883	3.9
	Simeprevir	13 940	2.0	11 296	2.0
5 years	Telaprevir	15 927	5.5	20 944	11.0
	Boceprevir	22 331	10.9	15 323	5.4
	Simeprevir	19 261	5.5	16 831	5.5
10 years	Telaprevir	21 756	9.1	28 970	9.0
	Boceprevir	30 609	18.2	20 718	18.3
	Simeprevir	23 706	9.1	21 468	9.1

Table 4. Cost-effectiveness ccoefficients and incremental cost-efficacy coefficients for combined treatment with DAA in treatment-naïve patients with CHC

Time period	DAA	CER	ICER
1 year	Telaprevir	4 555	
	Boceprevir	3 161	1 767
5 years	Telaprevir	2 916	
	Boceprevir	2 040	1 168
10 years	Telaprevir	2 403	
	Boceprevir	1 681	967

As Table 4 shows, the least cost-effectiveness coefficient was observed in case of combined treatment with boceprevir. Hence, this technology should be considered as dominating in treatment-naïve patients.

3.4 Cost-utility Analysis

Results of pharmacoeconomic cost-utility analysis are presented in the Table 5.

As Table 5 shows, treatment with boceprevir is less expensive and more effective in comparison with alternative schemes for a group of patients previously unsuccessfully treated at all time horizons. Thus, treatment with boceprevir is a strongly dominating technology for such a group of patients.

For group of patients previously untreated, treatment with telaprevir and simeprevir during 1 year and 5 years resulted in the same values of QALYs equal to 1.5 and 4.2, respectively. Thus, for horizons of 1 year and 5 years, the treatment with simeprevir was excluded from analysis as more expensive technology in comparison with telaprevir-based one.

Further, cost-utility ratio (CUR) and incremental cost-utility ratio (ICUR) were calculated for the group of treatment-naïve patients with hepatitis C (Table 6).

Table 5. Results of pharmacoeconomic cost-utility analysis of DAAs usage in combined treatment (with use of pegylated interferons and ribavirin) of patients with CHC, who were unsuccessfully treated before

Time period	Group	Treatment-naïve patients		Treated patients	
	DAA	Costs (US dollar)	Quality adjusted life years (QALY)	Costs (US dollar)	Quality adjusted life years (QALY)
1 year	Telaprevir	8 951	1.5	11 363	1.5
	Boceprevir	12 422	3.0	8 883	3.0
	Simeprevir	13 940	1.5	11 296	1.5
5 years	Telaprevir	15 927	4.2	20 944	4.1
	Boceprevir	22 331	8.4	15 323	8.5
	Simeprevir	19 261	4.2	16 831	4.2
10 years	Telaprevir	21 756	6.9	28 970	6.8
	Boceprevir	30 609	13.9	20 718	14.1
	Simeprevir	23 706	7.0	21 468	6.9

Cost-utility ratio was calculated as a ratio of cost difference and utility difference (quality adjusted life years) for therapeutic schemes studied. Incremental cost-utility ratio (ICUR) was calculated according to the following formula:

ICUR = Cost2 – Cost1/U2 – U1, where Cost is costs for CHC treatment, U is utility.

Table 6. Cost-utility ratio and incremental cost-utility ratio for combined therapy with DAA in treatment-naïve patients with CHC. Horizons were 1 year and 5 years

Time period	DAA	CUR	ICUR
1 year	Telaprevir	5 962	
	Boceprevir	4 112	2 285
5 year	Telaprevir	3 827	
	Boceprevir	2 660	1 512

According to data shown in Table 6, the least value of cost-utility ratio is observed for combined treatment with boceprevir. Therefore, this technology should be considered as dominating for treatment-naïve patients with chronic hepatitis C. Incremental coefficient shows additional costs per additional year of quality-adjusted life.

For a time period of 10 years, the linkage between therapy costs and its efficacy was not obvious. This is confirmed by cost-utility ratios for each preparation and calculation of incremental coefficients (Table 7).

Table 7. Cost-utility ratios and incremental cost-utility ratios for combined treatment of CHC patients previously untreated with DAA. The time horizon was 10 years

Time period	DAA	CUR	ICUR
10 years	Boceprevir	2 194	
	Simeprevir	3 407	987
	Telaprevir	3 161	26 114

Incremental coefficient shows necessity of additional cost for additional quality adjusted life year. Usage of telaprevir-based therapy instead of simeprevir-based therapy requires additional $26 114 per year QALY. In this case, incremental coefficient for the pair of boceprevir and simeprevir is equal to $987 (Fig. 3). In other words, the therapeutic schemes with boceprevir and telaprevir usage represent slightly dominating technologies in comparison with therapy with simeprevir. Therefore, it was possible to exclude simeprevir-based therapy from further consideration.

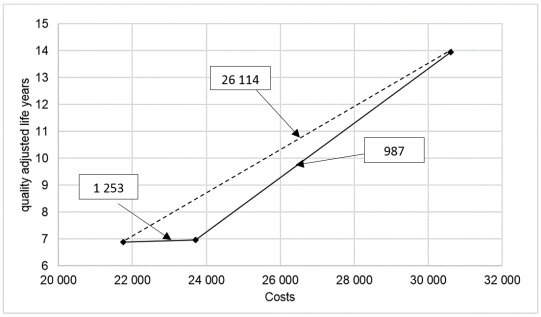

Fig. 3. Incremental cost-utility ratios for combined treatment with DAA in treatment-naïve patients with CHC for the time horizon of 10 years

As Table 8 shows, the least value of the cost-utility ratio was observed for combined treatment with boceprevir. Therefore, this technology should be considered as dominating in case of treatment-naive patients with hepatitis.

Table 8. Cost-utility ratios and incremental cost-utility ratios for combined treatment with DAA in CHC treatment-naïve patients for the time horizon of 10 years. Simeprevir-based treatment was excluded

Time period	DAA	CUR	ICUR
10 years	Boceprevir	131654	
	Telaprevir	189632	75173

According to the World Bank, annual GDP value per capita in Russian Federation was $8 447 in 2014. Willingness-to-Pay (WTP) Threshold value calculated with the use of GDP value in 2014, is equal to 3 × $8 447 = $25 341. So, the QALY costs in therapy with boceprevir do not exceed Russian Willingness-to-Pay Threshold.

4. CONCLUSION

Pharmacoeconomic analysis of chronic hepatitis C viral infection treatment showed that the best combination of costs and effectiveness was observed in combined treatment with the use of pegylated interferon, ribavirin and boceprevir in treatment-naïve patients as well as patients with unsuccessful treatment experience. Thus, the combined therapy with the use of boceprevir is the most pharmacoeconomically justified in comparison with telaprevir and simeprevir-based treatment.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/16215