

**PHARMACOECONOMIC ANALYSIS OF THE TREATMENT OF CHRONIC
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ABSTRACT

The article provides a pharmacoeconomic analysis of the treatment of chronic hepatitis "C". The absence of serious anti-epidemic measures, such as hepatitis "C" vaccination, is analyzed.

KEYWORDS. Cirrhosis, chronic disease, anti-epidemic measure.**INTRODUCTION**

According to the WHO Newsletter (July 2016), 130–150 million people are affected by chronic hepatitis C infection worldwide, and about 3% of the world's population are infected with the disease. A characteristic feature of this disease is the high frequency of chronicity, ranging from 50 to 85% of acute forms of hepatitis C. Subsequently, from 20 to 30% of cases of chronic hepatitis C (CHC) results in cirrhosis of the liver and the development of hepatocellular carcinoma, from which approximately 700,000 people die every year.^[1,2] In addition, the absence of serious anti-epidemic measures, such as vaccination, against hepatitis C, as well as in most cases the asymptomatic course of the disease, leads to an annual increase in the number of infected people worldwide.

Uzbekistan belongs to hyperendemic regions in terms of the prevalence of this virus infection with different levels of circulation in the regions, which, apparently, is associated with medical and social conditions (features in the number of families, age structure) and ethnic lifestyle of the indigenous population. studies revealed that among the examined healthy population of our country, 5.6% had anti-HCV and 8.3% had HBsAg.^[3,4]

In Uzbekistan, as in other countries of the post-Soviet space, a contradiction is revealed between the need to follow the modern level of therapy, which involves the use of new, usually expensive methods and drugs, and the constant lack of funding for healthcare. Therefore,

under the current conditions, it is very important to analyze the economic feasibility of using antiviral and hepatotropic drugs from various clinical and pharmacological groups, taking into account the breadth of their prevalence in real clinical practice, as well as their therapeutic efficacy and safety, which was the purpose of our study.

MATERIAL AND METHODS

The study was undertaken on 112 patients with chronic hepatitis C who received inpatient treatment at the Bukhara Multidisciplinary Hospital in 2012-2014 and then were examined during the next 3 years during the process of outpatient treatment.

For all patients, upon admission, then regularly after 10 days, conventional biochemical blood tests were performed. A comprehensive examination of patients included the determination of indicators of cytolytic, hepatosuppressive, mesenchymal-inflammatory and cholestatic syndromes.

An etiological diagnosis was made based on the results of an enzyme-linked immunosorbent assay (ELISA). Diagnostic sets "DS" (Nizhny Novgorod, Russia) were used as test systems to detect antibodies to HCV in blood serum and to detect HBsAg.

To establish the fact of eradication, molecular genetic studies were performed using PCR analysis. DNA was extracted from whole blood using the DNA-Sorb test

system (Interlabservis, Russia). For PCR testing, RotorGene 6000 (CorbettResearch, Australia) and reagent kits (Synthol, Russia) were used.

RESULTS AND DISCUSSION

As known, pharmacotherapy of any disease is divided into etiotropic, pathogenetic and symptomatic according to their importance. Therefore, before treatment, it is important to identify the etiological causes of the disease. Regarding chronic liver diseases, they are divided into viral and non-viral. The former are mainly caused by hepatitis B and C. The etiology of non-viral hepatitis, according to the literature, may be alcoholic, toxic, drug, autoimmune and unknown. Moreover, the last two are quite rare with the same prevalence in all populations, not exceeding 5-6% of the number of non-viral hepatitis, and the rest are toxic in nature.^[5,6]

In this regard, the etiotropic therapy of chronic hepatitis is for viral etiology - in the appointment of antiviral drugs, and for toxic - in the cessation of exposure to the relevant chemicals.^[7,6] Whereas, pathogenetic therapy is independent of the etiological factor and is mainly carried out by hepatoprotectors.

The choice of other drugs, except for antiviral therapy, in the complex treatment of patients with chronic viral hepatitis is selected individually in each case, taking into

account the course of diseases and complications and must meet the criteria corresponding to a high level of evidence in order to prevent unreasonable irrational use of drugs.

According to the literature, the effectiveness of hepatoprotectors is not the same for various pathological syndromes observed in chronic hepatitis (CG) and liver cirrhosis (CP).^[5,8,9] As can be seen from table 1, with a cytolytic syndrome accompanied by an increase in the enzymes AST and ALT, essentielle and karsil are most effective, with cholestatic syndrome - UDCA, and synthetic deficiency - liv-52 and heptral. However, essentielle and UDCA turned out to have a wider spectrum of action and showed its positive effect in synthetic and hepatic cell failure.

Depending on the etiological causes of chronic hepatitis C, these syndromes occur to varying degrees. According to our data, with exacerbation of viral CG, the predominant clinical syndrome is cytolytic, and more than half of cases for hepatitis B are more pronounced. Moreover, the latter often manifests itself both in isolation and in combination with cholestatic syndrome, while chronic hepatitis C occurs in almost half of cases without the manifestation of laboratory-significant syndromes.

Table 1: The effect of various hepatoprotectors on some pathological syndromes in liver diseases.

№	drugs	Cytolytic (AST, ALT)	Cholestatic (bilirubin, alkaline, phosphatase, GGT)	Synthetic deficiency (decreased albumin, prothrombin, fibrinogen)	Hepatic cell failure
1	Essentiale	++	0	+	+
2	Ursodeoxycholic acid	±	++	+	+
3	Heptral	±	±	++	0
4	Liv.52	±	0	++	0
5	Legalon, carsil (silymarin)	++	0	+	±

When analyzing the ratio of different groups of drugs used to treat viral chronic hepatitis C in our preliminary studies, in the Bukhara region, there was a lack of antiviral drugs because of their high cost, while the most commonly prescribed group were infusion solutions with a detoxifying effect, hepatoprotectors and metabolism. At the same time, drugs containing essential phospholipids were prescribed as hepatoprotectors in more than half of the cases, UDCA (ursosan) in a quarter of the cases, the rest were carsil, bodice-52, apcasul and heptral.

According to the recommendations of some authors^[10], the presence of severe liver steatosis in viral hepatitis C causes the use of essential phospholipids until the process is resolved. Against the background of moderate activity of the cytolytic process without cholestasis, treatment begins with parenteral use of essential phospholipids or ademethionine, but in the future for long-term treatment, ursosan 10 mg / kg / day or essential phospholipids are recommended (end of the

course of therapy 1 month after normalization of the cytolytic syndrome).^[11,12] The main indication for ursosan is the presence of cholestasis, but this drug is necessary even with a combination of cholestasis and cytolytic syndrome. At the same time, according to a number of leading Russian hepatologists, in case of viral liver lesions when antiviral therapy is not possible, ursosan at a dose of 10 mg / kg / day for ≥ 6 months is the optimal drug due to the pronounced anti-inflammatory and immunomodulating effect.^[10,12, 13] In general, the variety of pathogenetic effects of ursosan makes it practically indispensable for chronic liver diseases, especially considering its antifibrotic properties.^[13-15]

In preliminary studies, we were able to develop a scheme of differentiated therapy of chronic hepatitis with the predominance of cholestatic syndrome based on compliance with the dependence of daily dosage ursosan on the results of a number of laboratory indicators reflecting the degree of cholestasis. At the same time, it was possible to reduce the overall course dose of ursosan

with mild, medium and severe degrees of cholestatic syndrome, respectively, by 73.4%, 52.6% and 39.7% relative to the traditional scheme, i.e. the effectiveness of the course of the drug had back. In general, differentiated therapy of patients with chronic hepatitis cholestatic syndrome, contributed to a decrease in the volume of the drug's use of treatment and actual reduce treatment time by almost 3 months.

However, with the above regimens of treatment treatment still does not occur and therapy of chronic hepatitis, as well as its complications should continue for a long time, possibly the rest of life. The reason for this may be the lack of antiviral drugs in the treatment regimens for chronic viral hepatitis C, which are specified in the standards of treatment, but the practice is not always carried out because of their high cost and inaccessibility.

According to the recommendations, the treatment of hepatitis C is not always effective drugs - Ribapirin and Interferon. months, depending on the genotype of the virus, using an injectable pathway of administration. Drugs have a number of side effects, and the course of treatment does not guarantee recovery due to frequent recurrence of the disease.

In part, this is due to the variation in hepatitis C genotypevirus depending on countries and areas of ethnic origin. Chronicization of the disease, response to antiviral treatment and progression of cirrhosis of the liver vary depending on the genotypes, which forces the doctor to individualize treatment and identify the degree of risk associated with the disease. The treatment scheme for hepatitis C it is usually developed based on the genotype of the virus and the condition of the liver, taking into account past therapy experience and test results.

The first antiviral drug patented to treat hepatitis C was Sofosbuvir (SOF), when it was registered in the U.S. and Europe in 2013 under the trade name Sovaldi. This drug is unique in that it has a direct effect on viruses, without affecting the cells of the human body and not reducing the level of natural protection - immunity. The duration of treatment with these drugs is on average 12 weeks.

The use of such a drug in 90% of cases guarantees a complete cure for hepatitis C. Until some time, its widespread use limited a very high cost. However, the problem was solved by the development of Gilead technology for making cheaper analogues - generics, because the time of its patent protection was over.

At the same time, the United States granted the right to manufacture licensed funds to 11 Indian enterprises with a guarantee of the quality of Indian counterparts and the control of the license holder of the price policy for Indian generics. Sofosbuvir has become produced in India under the name Hepcvir and Hepcinat. The list of countries that

are now allowed to export this drug is limited to the United States by 91 countries with a high incidence of hepatitis C, where even Russia did not get. Therefore, patients from other countries are forced to purchase this product by ordering through online stores or buy in pharmacies in India as part of drug tourism.

The second newest and most powerful drug, Daclatasvir (DCV), which causes the inhibition of the hepatitis C virus protein, was patented under the name Ducklinza. The drug is active against 1, 2 and 3 and 4 genotypes of the virus and prevents the spread in the blood. In 2015, the European Commission on Drugs tested and approved this drug for release to the international market, and in India launched the process of Daklatesvir's analogues, Daklavir and Nadtak, whose clinical trials have shown 90-98% cure.

Hepatitis treatment with Indian generics has a number of benefits:

The possibility of using generics even after a recurrence of the disease, with unsuccessful therapy with Ribavirin (RBV);

Significant reduction in treatment;

The drug is taken in pill form once a day;

Low chance of side effects;

There is a huge probability of a full recovery.

Naturally, Indian generics, as well as all medicines, have a number of contraindications:

The age of the patient under the age of 18 (no clinical trials were conducted in this age range);

Individual intolerance to individual components

The last stages of cirrhosis

Pregnancy

Lactation period

Liver transplantation.

However, the high effectiveness of new antiviral drugs, approaching 100%, as well as the conditionality of the submitted contraindications, due only to the lack of complete information and under-examination of these drugs at present, accordingly, the latest publications give hope for the full eradication of the hepatitis C virus from the human population, as well as WHO's planning to reduce the incidence of hepatitis C by 2030 and nearly 3 times the mortality from its effects worldwide.^[20,22,23]

Currently, to achieve higher efficacy of therapy, not one, but a combination of antiviral drugs is used. To select the most optimal drug regimen, it is customary to conduct a pharmacoeconomic analysis with the calculation of the effectiveness of treatment and its corresponding cost.

Thus, according to a number of authors^[24], due to the lack of unambiguous results on the effectiveness of hepatitis C treatment with the PegIFN- α + RBV scheme in patients who previously received HTP, this scenario was stopped at the stage of pharmacoeconomic efficiency analysis. According to their data, it was found that treatment regimens DCV) + SOF and DCV + SOF +

RBV are considered dominant in terms of cost-effectiveness analysis compared with SOF + RBV in groups of patients with chronic hepatitis C, respectively, without cirrhosis and cirrhosis. At the same time, the analysis of "budgetary impact" showed that the transition to the use of DCV + SOF and DCV + SOF + RBV instead of SOF + RBV will not only not require additional costs for antiviral therapy, but will also reduce the cost of medical care for patients.

According to Jietal.^[25], the combination of the antiviral drugs sofosbuvir + daclatasvir provides a high rate (95%) of eradication of the virus in patients with genotype 1 HCV. According to the data obtained, the optimal treatment duration according to the sofosbuvir + daclatasvir regimen without ribavirin is 12 weeks. in patients without cirrhosis and 24 weeks. - with cirrhosis.

Therefore, to date, new highly effective antiviral drugs have begun to enter the medical market, which can quite successfully achieve the complete eradication of the hepatitis C virus. Moreover, since they are generics, they become more and more affordable for the general population at a price.

Given this information, we decided to undertake a pharmaco-economic study on the treatment of patients with chronic viral hepatitis "C" with an assessment of the effectiveness and cost of the course of treatment. It is known that for effective therapy, a combination of generics with hepatoprotectors and immunomodulators is required. In order to rationally select the latest drugs, the

use of Ursodeoxycholic acid - ursosan, combining both hepatoprotective and immunomodulating properties, was proposed as the most optimal. In addition, the main property of ursosan is the anticholestatic syndrome, the syndrome of which was most often detected among the patients examined by us, and their treatment was started during the period of exacerbation of the disease with a predominance of one or another syndrome.

As shown in table 2, the use of a standard course of treatment on the basis of essentials in chronic viral hepatitis C with manifestations of cholestatic syndrome costs about one million soums per patient. Moreover, if on average three cases of exacerbations occur in three years and in 12% hepatitis goes into cirrhosis, then even without taking into account the treatment of cirrhosis, the costs for three years will amount to 2.6 million soums. The use of ursosan in a similar case in a standard dosage slightly reduces the frequency of hospitalizations and more than halves the development of cirrhosis, which together can make up a lower three-year cost of treatment, i.e. for conducting 2 courses of treatment for 3 years.

The use of a differentiated dosage of ursosan in these cases can cost as little as 280,000 sum per patient with almost the same treatment effectiveness. When carrying out this treatment option for three years, on average, 2 cases of exacerbations occur and up to 5% of hepatitis goes into cirrhosis, so even without taking into account the treatment of cirrhosis over three years, costs can be as little as 560,000 sums.

Table 2: Pharmaco-economic assessment of the cost of treating chronic hepatitis C with existing and proposed regimens.

№	Treatment regimens	Number of hospitalizations per year	Transition to cirrhosis over a 3-year period	The cost of the course of treatment (in sum) for the first year	The cost of the course of treatment (in sum) for three years
1	Hepatoprotectors (essentiale) (6 month)	1,1	12%	864000	2592000
2	Ursosan in a standard dosage (6 month)	0,7	4,5%	770000	1540000
3	Ursosan in an individual dosage (3 month)	0,7	5%	280000	560000
4	Ursosan in the proposed dosage + antiviral preparations (sofosbuvir \ daclatasvir) (3 month)	0	0	280000+ 1040000 = 1320000	1320000

Using a treatment regimen that includes a three-month oral course of antiviral drugs (sofosbuvir / daclatasvir) worth 10,000,000 soums with the addition of a different dosage of treatment with ursosan in the detection of cholestatic syndrome costs 1,332,000 soums per patient. As a result of such a course of treatment, no patient at the end of the 3-month period revealed hepatitis C virus based on PCR analysis. Moreover, this was not observed during the next 3 years of observation. Not a single patient treated during this period was treated or hospitalized due to exacerbations of the disease, nor was there a clinic for the transition of chronic hepatitis to cirrhosis of the liver.

Therefore, in general, the cost of one course of treatment with the complex of antiviral drugs and ursosan in the amount of 1320000 soums remains as the cost for 3 years of observation and this is a cheaper treatment option regarding the use of essentials or ursosan in a standard dosage and, moreover, with a more favorable result.

The above arguments are evidence of the economic viability of performing antiviral therapy for chronic hepatitis C by combining generics with hepatoprotectors, in particular, ursosan with the combination sofosbuvir \ daclatasvir. At the same time, the cost of antiviral drugs fully pays off by saving the total losses for the treatment

of chronic hepatitis C with other drugs, for example, hepatoprotectors such as essential phospholipids. Since currently the treatment of chronic hepatitis C with essentials or ursosan in a standard dosage is quite affordable for patients of a wide range of people, the cost of a comprehensive treatment of close importance is also considered to be well available.

Findings

- Differential administration of ursosan with various starting dose options and their gradual reduction during treatment in patients with chronic hepatitis C with the detection of cholestatic syndrome led to a reduction in treatment time by almost 3 months.
- Conducting a joint course of treatment with antiviral drugs for patients with chronic hepatitis C: daclatasvir + sofosbuvir and differentiated administration of ursosan led to a complete stabilization of the clinical picture with no exacerbations and cases of transition to liver cirrhosis in the next 3-year period.
- The cost of treating chronic hepatitis C with a complex of antiviral drugs and ursosan for 3 years of observation is the cheapest treatment option regarding the use of essentials or ursosan in a standard dosage.

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