



Effectiveness of antiviral treatment of patients with chronic hepatitis C GT 1b depending on the presence of comorbid chronic renal insufficiency

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Aim. The aim of the work was to analyze the effectiveness of antiviral therapy (3D mode) in patients with chronic hepatitis C (CHC) GT1 in clinical practice, depending on the presence of comorbid chronic renal insufficiency stage V, who receiving hemodialysis.

Materials and methods. 101 patients with CHC GT1 who received antiviral therapy (AVT) according to the scheme OBV/PTV/r + DSV ± RBV (3D-mode) during 12 weeks were included in the study. All patients with CHC were divided into two groups depending on the presence of comorbid chronic renal insufficiency (CRI): 92 patients who did not have accompanying CRI and 9 patients with comorbid CRI stage V who received program hemodialysis.

Results. The effectiveness of antiviral therapy in patients with CHC GT1 according to the OBV/PTV/r + DSV ± RBV scheme in clinical practice was high in terms of the achievement of 12 weeks sustained virologic response (SVR 12) SVR 12 (94.1 %). The frequency of achieving SVR 12 in CHC patients without concomitant CRI was 94.6 %, and with of comorbid CRI stage V (hemodialysis) – 88.9 % and had not statistically significant differences ($P > 0.05$). Treatment according to the 3D-mode was accompanied with stable normalization of ALT activity in 86.0 % of patients with CHC, and the frequency of it is achievement did not depend on the presence of comorbid CRI stage V (100.0 % vs. 85.2 % in patients without the specified concomitant pathology, $P > 0.05$).

Conclusions. The effectiveness of antiviral therapy in patients with CHC GT1 according to the OBV/PTV/r + DSV ± RBV scheme in clinical practice is high in terms of the achievement of SVR 12 (94.1 %) and does not depend in the presence of comorbid CRI stage V in the patient (94.6 % vs. 88.9 %, $P > 0.05$). The severity of liver fibrosis does not affect the effectiveness of AVT in patients with CHC GT1 in the presence of comorbid CRI stage V and without this comorbid condition.

Key words: chronic hepatitis C, viral infection, comorbidity, chronic renal insufficiency, hemodialysis, antiviral treatment.

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Ефективність протівірусного лікування хворих на хронічний гепатит С GT 1b залежно від наявності коморбідної хронічної ниркової недостатності

Г. В. Веницька, О. В. Рябоконт

Мета роботи – проаналізувати ефективність протівірусної терапії (3D-режим) в клінічній практиці у хворих на хронічний гепатит С (ХГС) GT1, які отримують гемодіаліз, залежно від наявності коморбідної хронічної ниркової недостатності V стадії.

Матеріали та методи. У дослідження залучили 101 хворого на ХГС GT1, які отримували протівірусну терапію (ПВТ) за схемою OBV/PTV/r + DSV ± RBV (3D-режим) тривалістю 12 тижнів. Залежно від наявності коморбідної хронічної ниркової недостатності (ХНН) усіх хворих на ХГС поділили на групи: 92 пацієнти, які не мали супутньої ХНН, та 9 осіб із коморбідною ХНН V стадії, котрі отримували програмний гемодіаліз.

Результати. У результаті дослідження доведено, що ефективність ПВТ у хворих на ХГС GT1 за схемою OBV/PTV/r + DSV ± RBV у клінічній практиці виявилася високою за показником досягнення 12-тижневої стійкої вірусологічної відповіді (СВВ 12) – 94,1 %. Частота досягнення СВВ 12 у хворих на ХГС без супутньої ХНН становила 94,6 %, а в разі коморбідної ХНН V стадії (гемодіаліз) – 88,9 %, не мала статистично значущих розбіжностей ($p > 0,05$). Лікування за 3D-режимом супроводжувалося стійкою нормалізацією активності АлАТ у 86,0 % пацієнтів із ХГС, а частота її досягнення не залежала від наявності коморбідної ХНН V стадії (100,0 % проти 85,2 % у хворих без цієї супутньої патології, $p > 0,05$).

Висновки. Ефективність ПВТ хворих на ХГС GT1 за схемою OBV/PTV/r + DSV ± RBV у клінічній практиці є високою за показником досягнення СВВ 12 (94,1 %) і не залежить від наявності у пацієнта коморбідної ХНН V стадії (94,6 % проти 88,9 %, $p > 0,05$).

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Key words: chronic hepatitis C, viral infection, comorbidity, chronic renal insufficiency, hemodialysis, antiviral treatment.

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Ступінь виразності фіброзу печінки не впливає на ефективність ПВТ у хворих на ХГС GT1 і при коморбідній ХНН V стадії, і без цього коморбідного стану.

Ключові слова: хронічний гепатит С, вірусна інфекція, коморбідність, хронічна ниркова недостатність, гемодіаліз, протівірусне лікування.

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Chronic hepatitis C (CHC) is a widespread viral infection and one of the main causes of liver cirrhosis and hepatocellular carcinoma [1]. According to World Health Organization (WHO) estimates, between 500 million and 1 billion people are infected with hepatitis C virus (HCV). The prevalence of chronic liver disease associated with HCV is currently about 200 million and 3–4 million new infected people join to them every year [2]. According to EASL experts, despite the availability of effective treatment regimens using direct antiviral drugs about 400000 people die annually from liver diseases associated with CHC [3]. According to the Center of Public Health of Ukraine, as of January 1, 2019, 3.6 % of the Ukraine population had a confirmed diagnosis of CHC, which indicates an average level of infection [2,4].

The main risk groups for HCV-infection are recipients of blood and their components, persons who receive invasive procedures for a long time, in particular, hemodialysis [5,6]. World experience shows that there is a high probability of infection with the hepatitis B virus and HCV precisely under the condition of receiving hemodialysis [7]. Data from the literature show that in European countries, the prevalence of HCV-infected patients in hemodialysis centers ranges from 2 % to 34 %. The lowest rate of infection is in Great Britain – 2 % and Switzerland – 5.7 %, and the highest rates are in Italy – 27 %, Poland – 29 % and Romania – 34 % [8–10]. In Saudi Arabia, when analyzing the prevalence of HCV-infection among patients of hemodialysis centers, it was found that 41.9–45.5 % of patients have positive anti-HCV. This was explained by a long stay on systemic hemodialysis (>4 years) and previous blood transfusions (>5) [11,12]. In Japan, the frequency of detection of anti-HCV was analyzed in patients with chronic renal insufficiency (CRI) stage V based on 18 hemodialysis centers. It was found that 22.2 % were seropositive, and the prevalence of HCV-infection clearly depended on the hemodialysis duration [13]. Numerous researchers of this problem are sure that 90–95 % of patients who initially enter program hemodialysis do not have hepatitis markers, and infection occurs only during their treatment [10,14–16].

In Ukraine, the frequency of anti-HCV detection among patients in specialized departments of various profiles is about 6.9 %, while in the dialysis population this indicator is almost 4 times higher – 27.5 % [16]. An analysis of the frequency of infection with viral hepatitis in hemodialysis units under the state program in Ukraine was conducted. It was found that 61.4 % of patients had blood-contact viral hepatitis markers (HBsAg – 16.4 %, anti-HCV – 45.0 %). It was proven that the length of patients stay on programmed hemodialysis has a direct relationship with the frequency of viral hepatitis markers detection. If the treatment time is up to 1 year, then

infection was determined in 38.4 % of patients, and with hemodialysis for 2–3 years – in 59.2 % of patients, and with hemodialysis for more than 5 years – in 68.8 % of patients. At the same time, HCV monoinfection was detected in 17.4 % of patients who were treated with programmed hemodialysis for up to 1 year, and in 40.6 % of patients with a duration of hemodialysis more than 5 years [10]. A clear correlation is observed between the level of HCV-infection and the number of received hemodialysis sessions. A statistically significant difference in the frequency of infection with hemocontact viral hepatitis is observed in groups of patients who received up to 50 sessions, from 50 to 200 and more than 200 sessions of hemodialysis. After 200 program hemodialysis procedures (approximately after 2 years), 57.5 % of patients were found to be anti-HCV positive [16].

Comorbidity of CHC and CRI stage V, who receive hemodialysis, aggravates the course of the main and comorbid diseases [14,15]. According to data from a meta-analysis of seven observational studies, which included 11 589 patients with CRI stage V and received programmed hemodialysis, a statistically significantly higher mortality rate was recorded among patients seropositive for anti-HCV than among patients without concomitant HCV. Even, in these patients liver cirrhosis and hepatocellular carcinoma were identified as one of the main causes of death [14,17].

With the advent of new antiviral drugs with a direct mechanism of action, the implementation of the WHO global strategy became possible. The purpose was to eliminate agents of viral hepatitis as a threat to public health [2]. Due to significant changes in the strategy of antiviral therapy (AVT) of patients with HCV from interferon-containing to interferon-free regimens [18–21], the possibility of the HCV micro-elimination has appeared in certain groups of patients, in particular and in patients with CRI stage V receiving programmed hemodialysis [22–25].

Previously, in presence of only interferon-containing regimens, the treatment of HCV patients with comorbid CRI was significantly limited. It is known that with normal kidney function, the half-life of interferon after subcutaneous injection is about 2–4 hours. Then filtration in the glomeruli of the kidneys followed by reabsorption in the tubules of the kidneys, where proteolytic degradation of the molecule occurs. Kidneys have the main role in the metabolism of interferon [18,19]. In patients with CRI stage V who receive hemodialysis, there is a significant violation of the removal of the interferon molecule and its accumulation. This provokes the appearance of serious side effects and makes it impossible to conduct interferon-containing therapy [18–20].

The emergence of interferon-free treatment regimens, namely the 3D-mode, made it possible to perform AVT

in patients with CHC GT1 with comorbid CRI stage V who are receiving hemodialysis [21–26]. The 3D regimen is a combination of ombitasvir (OBV), paritaprevir boosted with ritonavir (PTV/r) and dasabuvir (DSV), with the addition of ribavirin (RBV) in CHC patient with severe liver fibrosis (F 3–4). The mechanism of action of ombitasvir, paritaprevir and dasabuvir consists in inhibition of non-structural protein 3/4 A protease and the ability to inhibit non-nucleoside polymerase of non-structural protein 5B, respectively. The combination of these active substances makes it possible to achieve high AVT efficiency in patients from difficult categories, for example, with liver cirrhosis and after liver transplantation [27]. The antiviral activity of paritaprevir is enhanced due to the combination with ritonavir, which makes it possible to use the drug once a day and in a lower dosage. Paritaprevir is metabolized by cytochrome P450 (CYP) 3A4, and ritonavir is the main inhibitor of this enzyme [29]. HCV patients with comorbid CRI of any stage do not increase the exposure of these drugs with direct antiviral action to a clinically significant degree (changes <50 %), therefore, do not require dose adjustment [21,28].

According to randomized studies in the general population of CHC patients, the 3D-mode demonstrates high (>95 %) efficiency [27–29]. Therefore, today it is relevant to find out its effectiveness in everyday clinical practice, for example, in patients with hemodialysis.

Aim

The aim of the work was to analyze the effectiveness of antiviral therapy (3D mode) in clinical practice in patients with chronic hepatitis C GT1, depending on the presence of comorbid chronic renal insufficiency stage V, receiving hemodialysis.

Materials and methods

In the study 101 patients with CHC GT1 were included. There were examined and treated at the hepatological center of the Municipal Non-Profit Enterprise “Regional Infectious Diseases Clinical Hospital” of Zaporizhzhia Regional Council. The age ranged from 27 to 72 years, the median age was 54.0 (43.0; 61.0) years old, 45 men and 56 women were included in the study. Duration of CHC from the moment of laboratory confirmation of the diagnosis was 8.0 (2.0; 13.0) years. In all patients, GT1 HCV-infection was confirmed by the polymerase chain reaction (PCR) method and the viral load was determined before the start of treatment. The median viral load was 253 500 (48 333; 1 000 000) IU/ml. At the same time, a high viral load (>400 000 IU/ml) was detected in 39 (38.6 %), a low (<400 000 IU/ml) in 62 (61.4 %), respectively (EASL 2018). Necrotic-inflammatory activity in the liver was assessed by the level of increased alanine aminotransferase (ALT) according to the classification of chronic hepatitis (Los Angeles, 1994). The severity of liver fibrosis was determined for all patients based on the results

of the liver fibroelastometry. Severe liver fibrosis with transformation into liver cirrhosis F 3–4 was detected in 44 (43.6 %) patients, in 57 (56.4 %) patients stage of liver fibrosis F 0–2 was confirmed.

All patients were examined and received AVT according to the scheme OBV/PTV/r + DSV ± RBV (3D mode) lasting 12 weeks as part of the State target program in accordance with the Unified clinical protocol of primary, secondary (specialized) medical care, tertiary (highly specialized) medical care help with viral hepatitis C in accordance with the Order of the Ministry of Health of Ukraine No. 729 dated 18.07.2016. AVT efficacy was assessed per protocol at the end of treatment and at 12 weeks to assess sustained virologic response (SVR 12).

Depending on the presence of comorbid CRI, all patients with CHC were divided into groups: group I – 92 patients who did not have concomitant CRI, group II – 9 patients with comorbid CRI stage V, who were under the dispensary supervision of a nephrologist and received programmed hemodialysis lasting from 1 up to 14 years (7.2 years on average). Groups of patients did not differ statistically ($P > 0.05$) in terms of gender, age, and level of viral load before the start of treatment.

Statistical data processing was carried out in the program Statistica for Windows 13 (StatSoft Inc., No. JPZ804I382130ARCN10-J).

Results

According to the results of the study, it was established that the implementation of AVT according to the scheme OBV/PTV/r + DSV ± RBV was accompanied by the negation of HCV-RNA in the blood of most patients as early as the 4th week of treatment (95.1 %). This effect persisted even at the end of the therapy, however, when assessing the stability of the virological response, a certain decrease of this parameter was recorded to 94.1 %. A comparison of the frequency of achieving a virological response in CHC patients of the studied groups was made. It was shown that there was no statistically significant difference ($P > 0.05$) in the frequency of HCV-RNA negation in the blood during all observation periods. The frequency of achieving SVR 12 in CHC patients with the presence of comorbid CRI stage V was 88.9 % versus 94.6 % in patients without the specified concomitant pathology ($P > 0.05$) (Table 1).

The dynamics of ALT changes were analyzed, and it was showed – every third patient with HCV had a normal activity level of this enzyme in the blood. The comparative analysis showed that in patients with HCV with comorbid CRI stage V, the normal ALT level in the blood was recorded almost 2 times more often than in patients of group I, however, this difference was not statistically significant ($P > 0.05$). Subsequently, after 4 weeks of AVT in patients with HCV, an increase in the frequency of achieving ALT normalization from 36.6 % to 77.2 % ($P < 0.05$) was recorded, and at the time of AVT completion to 86.1% ($P < 0.05$). This result was maintained even at the time of SVR 12 assessment (86.0 %). A similar regularity in the dynamics of ALT activity normalization in

Table 1. The effectiveness of AVT (3D mode) in patients with CHC GT1 depending on comorbid CRI stage V, abs (%)

Terms observation	CHC patients (n = 101)	CHC patients	
		I group (n = 92)	II group (n = 9)
Negation of HCV-RNA in the blood			
After 4 weeks of AVT	96 (95.1 %)	87 (94.6 %)	9 (100.0 %)
At the time of AVT completion	96 (95.1 %)	87 (94.6 %)	9 (100.0 %)
At the time of the SVR 12 assessment	95 (94.1 %)	87 (94.6 %)	8 (88.9 %)
ALT activity normalization			
Before the start of AVT	37 (36.6 %)	31 (33.7 %)	6 (66.7 %)
After 4 weeks of AVT	78 (77.2 %) ¹	70 (76.1 %) ¹	8 (88.9 %)
At the time of AVT completion	87 (86.1 %) ^{1,2}	79 (85.9 %) ^{1,2}	8 (88.9 %)
At the time of the SVR 12 assessment	49 of 57 (86.0 %) ¹	46 of 54 (85.2 %) ¹	9 (100.0 %)

1: the difference is significant, compared to the indicator before the start of AVT in the corresponding group ($P < 0.05$); 2: compared to the indicator after 4 weeks of treatment in the corresponding group ($P < 0.05$).

Table 2. AVT virological response (3D mode) with different degrees of liver fibrosis in patients with CHC GT1 depending on comorbid CRI stage V, abs (%)

Observation periods	CHC patients (n = 101)		CHC patients		
			I group (n = 92)		II group (n = 9)
	F 0–2 (n = 57)	F 3–4 (n = 44)	F 0–2 (n = 48)	F 3–4 (n = 44)	F 0–2 (n = 9)
After 4 weeks of AVT	54 (94.7 %)	42 (95.5 %)	45 (93.8 %)	42 (95.5 %)	9 (100.0 %)
At the time of AVT completion	54 (94.7 %)	42 (95.5 %)	45 (93.8 %)	42 (95.5 %)	9 (100.0 %)
At the time of the SVR 12 assessment	53 (93.0 %)	42 (95.5 %)	45 (93.8 %)	42 (95.5 %)	9 (88.9 %)

the blood was noted in the I group of patients. The increase in the frequency of ALT normalization from 33.7 % to 76.1 % ($P < 0.05$), and at the time of AVT completion to 85.9 % ($P < 0.05$) with maintenance of this level 12 weeks after AVT termination (85.2 %). It should be noted that in all (100 %) patients with CHC with the presence of comorbid CRI stage V at the time of SVR 12 evaluation, the ALT activity remained at a normal level (*Table 1*).

According to the results of the virological response analysis in CHC patients with different liver fibrosis stages, it was established that the frequency of formation of SVR 12 did not depend on the liver fibrosis severity ($P > 0.05$) and amounted to 93.0 % in patients with stages F 0–2 and 95.5 % in patients with stages F 3–4. In patients with CHC of the group I who did not have comorbid CRI, this indicator was 93.8 % and 95.5 %, respectively ($P > 0.05$). In patients of the group II who had comorbid CRI stage V, liver fibrosis stages F 0–2 were determined, the SVR 12 frequency was 88.9 % and did not statistically differ from the corresponding indicator of the group I patients (*Table 2*).

Analysis of AVT side effects according to the scheme OBV/PTV/r + DSV ± RBV showed that in no case they did not need to stop AVT, and the frequency of occurrence did not differ statistically ($P > 0.05$) in patients of the studied groups. Thus, patients in the group I had thrombocytopenia (27 out of 92 – 29.3 %), skin itching (9 out of 92 – 9.8 %), and patients in the group II had skin itching and nausea (1 out of 9) in the first weeks of treatment (1 out of 9).

Discussion

Recently, in the modern literature, there are more and more studies on the use in clinical practice of interferon-free regimens in the treatment of CHC patients with comorbid CRI with an assessment of the effectiveness and safety of this AVT. In some cohort studies, even 100 % effectiveness of using the 3D mode has been demonstrated [22,26]. Thus, the authors [26], while observing CHC patients with CRI stages IV–V who received programmed hemodialysis, after treatment according to the OBV/PTV/r + DSV ± RBV scheme, noted the formation of SVR 12 in all patients (14 out of 14). In the study [22], the formation of SVR was also demonstrated in 100 % (25 out of 25) of HCV patients with comorbid CRI who received hemodialysis. At the same time, it was noted that already on the 4th week of treatment, HCV-RNA negation in the blood occurred [22]. In an American study [21], to assess the safety of the use of the 3D mode (in the treatment of patients with CHC GT1) and the 2D mode (in the treatment of patients with CHC GT4) was studied the impact effect of CRI in different stages on the pharmacokinetics of antiviral drugs, which are included in these regimens. According to the results of this study, it was confirmed that these treatment regimens do not require correction of the drugs dosage in the treatment of patients with CHC and with comorbid CRI in any degree [21].

The majority of studies of the use of 3D mode in clinical practice demonstrate very high efficiency, but not 100 % [23–25]. Thus, as part of the RUBY-1 study, the formation

of SVR 12 was demonstrated in 95 % (18 out of 19) of patients with CHC GT1 and comorbid CRI in the terminal stage [23]. 20 patients without liver cirrhosis were included in this study, and at the time of AVT completion, all patients had negative HCV-RNA in their blood. However, one patient died on day 14 after AVT completion as a result of systolic dysfunction unrelated to AVT, which did not allow SVR 12 assessment in this case. However, a 49 years old patient with F3 liver fibrosis relapsed 4 weeks after AVT completion [23].

Particular attention is drawn to the Spanish study [24], which was conducted 9 centers in Spain and aimed at evaluating the effectiveness of the 3D regimen in patients with HCV both with comorbid CRI and with normal kidney function. According to the results of the study, it was proved that there is no influence of comorbid CRI on the AVT effectiveness in patients with CHC GT1. At the same time, it is the group of CHC patients with comorbid CRI stages IV–V that pay our attention, of which 78.2 % received hemodialysis, 36.9 % of patients had liver cirrhosis, and 45.6 % additionally received RBV. Despite a significant number of patients with high stages of chronic renal insufficiency and severe liver fibrosis, SVR 12 was formed in 95.7 % of patients. At the same time, the researchers noted that during the entire period of AVT, kidney function remained stable, severe side effects were not recorded [24]. The results of our study also established the high efficiency of SVR 12 formation in patients with CHC according to the scheme OBV/PTV/r + DSV ± RBV in clinical practice according to SVR 12 achievement (94.1 %) and the lack of the AVT scheme effectiveness dependence on the presence in patients with CHC GT1 comorbid CRI stage V which receiving hemodialysis (94.6 % vs. 88.9 %, $P > 0.05$). In addition, the treatment side effects that occurred in patients of both studied groups did not lead to the need to stop treatment.

In a multicenter study [25], the absence of liver cirrhosis effect on the SVR 12 achieving was demonstrated. This study included patients with CHC GT1 and GT4 with liver cirrhosis (23 %) and without liver cirrhosis, but in the presence of comorbid CRI stages IV–V. The authors [25] note that SVR 12 was achieved in 95 % of patients, however, in 3 out of 66 patients, AVT was discontinued due to the occurrence of side effects. According to the results of our study, AVT side effects were registered in both studied groups: among patients with comorbid CRI and among patients without concomitant pathology. However, their appearance did not lead to treatment discontinuation. The results of our study showed no effect of liver fibrosis on the frequency of SVR 12 achieving, which is consistent with the data of the previous studies.

Conclusions

1. The AVT effectiveness in patients with CHC according to the scheme OBV/PTV/r + DSV ± RBV in clinical practice is high in terms of the SVR 12 achievement (94.1 %) and does not depend on the presence of comorbid renal insufficiency stage V (hemodialysis) in the patient (94.6 % versus 88.9 %, $P > 0.05$).

2. Conducting AVT (3D mode) is accompanied by stable ALT activity normalization in 86.0 % of patients with CHC, and the frequency of its achievement does not depend on the presence of comorbid renal insufficiency stage V (100 % versus 85.2 % in patients without the specified concomitant pathology, $P > 0.05$).

3. The frequency of SVR 12 achieving after a course of AVT (3D mode) in patients with CHC does not depend ($P > 0.05$) on the liver fibrosis level in both patient groups: with presence of comorbid renal insufficiency stage V and without this condition.

Prospects for further research. In our opinion, it is promising in further studies to determine the factors that affect the risk of recurrence in patients with HCV who received a course of interferon-free AVT regimens.

Conflicts of interest: authors have no conflict of interest to declare.

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