

## Virological and Morphological Efficiency of Different Anti-Virus Therapeutic Regimens for Patients With Chronic Hepatitis C

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### ABSTRACT

**INTRODUCTION:** Chronic hepatitis C (CHC) is a topical medical and social issue in Ukraine, despite of the high effectiveness of present antiviral therapy (AVT). The aim of the research is to evaluate the virological and morphological effectiveness of various therapeutic regimens of AVT in cases of CHC.

**MATERIALS AND METHODS:** 160 patients with CHC underwent AVT. Liver fibrosis (F) was evaluated using a fibro-test before and after treatment. According to the AVT therapeutic regimens the patients were divided into the following groups: group 1 (51 patients) - pegylated interferon- $\alpha$  (PEG-IFN) and ribavirin for 24-48 weeks; group 2 (34 patients) - sofosbuvir as well for 12 weeks; group 3 (74 patients) no PEG-IFN 12-week therapeutic regimen: sofosbuvir and

ribavirin (2 patients), direct antiviral drugs (DAD): sofosbuvir and ledipasvir (48 patients), sofosbuvir and daclatasvir (11 patients), and ribavirin as well (9 patients) for 24 weeks, sofosbuvir and velpatasvir (3 patients), together with ribavirin (1 patient), 3D therapy (ombitasvir/paritaprevir/ritonavir + dasabuvir) (1 patient).

**RESULTS:** In the group 1, a stable viral response (SVR) in 12 and 24 weeks was evidenced in 78.4% of the patients, in the group 2 - in 97.0%, in the group 3 - in 98.7%. A number of people with the most severe inflammatory and necrotic processes in the liver fibrosis (F3) decreased from 41.6 to 9.7% ( $p < 0.02$ ) at the end of the treatment in the presence of a significantly increased frequency of F0 (up to 84.6%). After treatment, in 61 examined patients, liver fibrosis reduction was evidenced in 54.1%, in 36.1% the degree of fibrosis did not change, and in 9.8% - fibrosis expansion was present.

**CONCLUSIONS:** Eradication of HCV does not ensure further progression of liver fibrosis.

**Key words:** Chronic hepatitis C; Liver fibrosis; Treatment; interferons; Direct antiviral drugs

### Abbreviations

CHC: chronic hepatitis C; AVT: antiviral therapy; PEG-IFN: pegylated interferon- $\alpha$ ; DAD: direct antiviral drugs; SVR: stable viral response; LC: liver cirrhosis; HCC: hepatocellular carcinoma; VL: viral load; F: fibrosis.

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### INTRODUCTION

Chronic hepatitis C (CHC) is an urgent medical and social issue<sup>[1-5]</sup>. Hepatitis C virus (HCV), which is replicated mainly in hepatocytes, is one of the main causes of liver cirrhosis (LC) and hepatocellular carcinoma (HCC)<sup>[6]</sup>. In Ukraine the incidence of HCV infection is not significant: about 5% of the population is affected by the virus,

but the actual rates of morbidity are significantly higher than official reports and in some socially deprived groups they are 40-60%<sup>[2,3]</sup>. Present antiviral therapy (AVT) is quite effective, but branded drugs are expensive. In order to facilitate patients' access to the treatment of this disorder, a "State target social program for prevention, diagnosis and treatment of viral hepatitis until year 2016" has been developed and implemented in Ukraine<sup>[1]</sup>.

The aim of the research is to evaluate the virological and morphological efficacy of various therapeutic regimens of AVT in cases of HCV in the patients residing in Ternopil region, Ukraine.

## MATERIALS AND METHODS

In 2013-2018, in Ternopil region 160 patients with chronic hepatitis C underwent etiotropic treatment upon the state-run program or privately financed. The diagnosis was verified by revealing anti-HCV, determining the virus genotype and viral load (VL) in PCR. Also chronic hepatitis B, autoimmune diseases were discounted. The share of males was 55.3%, of females - 44.7% ( $p < 0.05$ ); the patients' age was 20-60 years old, on average ( $43.1 \pm 9.3$ ) years old.

The degree of fibrosis (F) as well as the severity of inflammatory and necrotic processes in liver was determined by fibrotest twice (after treatment as well). AVT was carried out and evaluated according to the current clinical protocols approved by the Ministry of Health of Ukraine, taking into account the recommendations for treatment of hepatitis C (EASL, 2015, 2016)<sup>[2-5]</sup>. The VL was monitored over time before treatment, in 4, 12, 24 and 48 weeks after the treatment beginning (depending on the therapeutic regimen) and in 12-24 weeks after its completion; clinical and biochemical examinations were carried out monthly, or more often as the circumstance arises.

Patients with CHC were divided into the following groups according to the AVT regimens: group 1 (51 patients) received pegylated interferon- $\alpha$  (PEG-IFN) and ribavirin in cases of the 1<sup>st</sup> virus genotype for 48 weeks, the 2<sup>nd</sup> and the 3<sup>rd</sup> - for 24 weeks; group 2 (34 patients) sofosbuvir as well, the duration of treatment was 12 weeks; group 3 (75 patients) - no PEG-IFN: sofosbuvir and ribavirin (2 patients); sofosbuvir and lepisavir for 12 weeks in cases of the 1<sup>st</sup> HCV genotype (43 patients) and in cases of the 6<sup>th</sup> genotype (1 patient) - ribavirin as well (6 patients), sofosbuvir and daclatasvir for 12 weeks in cases of the 2<sup>nd</sup> and 3<sup>rd</sup> genotypes (9 patients); in cases of F3-F4 and non-typed HCV (5 patients) as well as the 3<sup>rd</sup> genotype (5 patients) - plus ribavirin for 24 weeks, sofosbuvir and velpatasvir in cases of non-typed HCV (2 patients) together with ribavirin (1 patient), 3D therapy (ombitasvir/paritaprevir/ritonavir + dasabuvir) for 12 weeks (1 patient).

The research was conducted following the ethical principles of international clinical bioethics. Statistica 6.0 was used for statistical analysis. Results were considered statistically significant at  $p \leq 0.05$ .

## RESULTS

The patients were divided according to their HCV genotypes: 1b was in 117 (73.1%) patients, 2 - in 3 (1.9%), 3 - in 11 (6.9%), 3a - in 17 (10.6%), 6 - in 1 (0.6%), the virus was not typed in 10 (6.3%) patients, the recombinant RF virus 2k/1b - in 1 (0.6%) patient. The VL before AVT ranged from  $10^4$  to  $10^7$  MU/ml.

11 patients, out of 51 patients with chronic hepatitis C of group 1, stopped treatment (1 patient - due to contraindications that were present during the therapy, the rest were 'non-responders'); at the end of the AVT and in 24 weeks the virus in blood was not revealed in 40 (78.4%) patients - a sustained viral response (SVR).

The SVR was achieved in 33 (97.0%) patients out of 34 patients of

group 2. The RNA of the virus was revealed in 1 patient at the end of the AVT, although its concentration was 3 times less than the initial rate; nevertheless, the SVR was achieved in 12 and 24 weeks.

In the group 3, the SVR was achieved in 74 (98.7%) patients; in 1 patient with F4 and non-typed HCV genotype, who received sofosbuvir and daclatasvir, in 12 weeks the RNA of the virus was still revealed in the same quantity as at the beginning of treatment; the therapy was stopped. Later, HCC was diagnosed. The direct antiviral drugs (DAD) were quite effective for the patients with severe fibrosis and liver cirrhosis (Child-Pugh, class A and B), whom PEG-IFN was contraindicated for. The side effects of AVT were significantly less common than in the patients of groups 1 and 2 ( $p < 0.05$ ).

The number of patients with the highest severity of inflammatory and necrotic processes in the liver (F3) at the end of treatment significantly decreased: from 41.6 to 9.7% ( $p < 0.02$ ) with a significant increase in the frequency of F0 (up to 84.6%).

Before treatment, F0 was present in 21 (13.1%) patients, F1 - in 22 (13.8%), F2 - in 49 (30.6%), F3 - in 33 (20.6%), F4 - in 35 (21.9%). After treatment, fibrotesting was performed for 61 (38.4%) patients. The analysis of individual dynamics of liver fibrosis proved that F3-F4 was present in 42.5% of the patients before the AVT, in 27.0% ( $p < 0.05$ ) - at the end of treatment. At the same time, in 33 (54.1%) patients the degree of liver fibrosis decreased, in 22 (36.1%) it was the same, and in 6 (9.8%) the increased fibrotic changes were evidenced (in 3 patients the degree of fibrosis could not be determined). That is, despite the eradication of HCV, almost half of the patients (44.1%) did not experience relapsed fibrosis (F2-F4), and the trend of positive dynamics was more often evidenced in the group of patients, who received PEG-IFN for a long time (63.9 vs. 54, 2%,  $p > 0.05$ ).

## DISCUSSION

According to the literature, the effectiveness of dual therapy (PEG-IFN and ribavirin) in CHC is on average 54-56%. Successful treatment largely depends on the HCV genotype. The disease caused by the 2<sup>nd</sup> and the 3<sup>rd</sup> genotypes of the pathogen, is treated the most effectively, the accuracy of medical treatment is 76-88%, the treatment of the 1<sup>st</sup> virus genotype is much less effective (less than 50%)<sup>[7,8]</sup>. Significant liver fibrosis also reduces the possibility of achieving SVR as the final result of AVT in cases of CHC.

The efficacy of AVT in cases of CHC in the examined patients was significantly higher (91.9%), probably because of taking sofosbuvir by some of them and a less severe liver fibrosis before treatment. In 1 of 3 patients, infected with HCV genotype 2, with F4 (subcompensated LC), relapses occurred twice after treatment with PEG-IFN and ribavirin for 24 weeks as well as after re-treatment with the same drugs for 48 weeks. A more profound examination of the patient revealed infection with a recombinant RF 2k/1b virus, which was difficult to diagnose and responded to treatment with PEG-IFN<sup>[9]</sup>. The patient underwent 3D therapy (ombitasvir/paritaprevir/ritonavir + dasabuvir) for 12 weeks and 2D-therapy (ombitasvir/paritaprevir/ritonavir) + sofosbuvir for 12 more weeks. In 12 or 24 weeks after the treatment the HCV RNA was not revealed in blood.

The attained data on the dynamics of liver fibrosis after AVT is consistent with the results of other researchers, who believe that even after the HCV eradication, an increased activity of perisinusoidal Ito cells and expression of proteins (Bcl-2) - apoptotic inhibitors that support fibrogenesis, mono- and polyclonal proliferation of astrocytes and B-lymphocytes with a high risk of B cell neoplasia and HCC, may remain unchanged<sup>[10]</sup>. Additionally, endogenous (steatosis) and exogenous (toxic-alimentary) factors can contribute to cirrhosis

development.

According to the literature, the eradication of HCV is associated with a low progression of liver fibrosis<sup>[11]</sup>; accordingly, early treatment prevents complications of CHC. At the same time, late relapses of HCV infection in case of insufficient therapy duration were reported in the patients with LC treated with daclatasvir and asunaprevir and having SVR within 24 weeks<sup>[12]</sup>. Perhaps this was associated with the lack of anti-fibrotic action of the interferon-free therapeutic regimens, in comparison with the interferon therapy, due to a significant reduction in the therapy duration despite a better antiviral effect<sup>[13]</sup>.

The presence of severe liver fibrosis in the patients with CHC is a significant risk factor for HCC development<sup>[14]</sup>. In the untreated patients with LC, HCC cases were present much more frequently than in those treated with PEG-IFN or DAD<sup>[15]</sup>; however, they also took place after eradication of the virus<sup>[16]</sup>. Interferon-free therapy for CHC did not alter the short-term risk of HCC<sup>[17]</sup> that implied the need for patient monitoring even after HCV eradication<sup>[14]</sup>.

## CONCLUSIONS

The virological efficacy of AVT in cases of CHC was quite high: with PEG-IFN and ribavirin - 78.4%, with sofosbuvir as well it increased to 97.0%, with DAD - to 98.7%. The patients infected with HCV genotype 2 need further examination to identify possible recombinant 2k/1b resistant to PEG-IFN therapy. In the treatment of these patients, it is advisable to use AVT regimens effective both in cases of the 1<sup>st</sup> and 2<sup>nd</sup> genotypes of the virus.

DADs proved to be effective in the patients with severe liver fibrosis and cirrhosis, whom PEG-IFN was contraindicated for. In the presence of SVR, only 54.1% of the CHC patients had relapsed liver fibrosis, in the rest (44.1%), the degree of fibrosis was the same or even progressed (9.8%). The HCV eradication does not guarantee subsequent fibrosis development that implies the further dynamic clinical monitoring of these patients and control of possible HCC, as well as the use of antifibrotic drugs.

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## REFERENCES

1. Ukrainian State target social program of prevention, diagnosis and treatment of viral hepatitis for the period till 2016. Approved by the decision of the Cabinet of Ministers of Ukraine. 2013; **29**: 61.
2. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. *J Hepatol* 2015; **63**(1): 237-64. [PMID: 25911335]; [DOI: 10.1016/j.jhep.2015.04.006]
3. European Association for Study of Liver; Asociacion Latinoamericana para el Estudio del Hígado. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol* 2014; **60**(2): 392-420; [DOI: 10.1016/j.jhep.2013.11.003]
4. European Association for Study of Liver. EASL Recommendations on Treatment of Hepatitis C 2015. *J Hepatology* 2015; **63**(1): 199-236. [PMID: 25911336]; [DOI: 10.1016/j.jhep.2015.03.025]
5. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2016. *J Hepatology* 2017; **66**: 153-194. [PMID: 27667367]; [DOI: 10.1016/j.jhep.2016.09.001]
6. Wang LS, D'Souza LS, Jacobson IM. Hepatitis C - A clinical review. *J Medical Virology* 2016; **88**: 1844-1855. [PMID: 27097298]; [DOI: 10.1002/jmv.24554]
7. El-Serag HB, Kunik M, Richardson P, Rabeneck L. Psychiatric disorders among veterans with hepatitis C infection. *Gastroenterology* 2002; **123**(2): 476-482.
8. Kowala-Piaskowska A, Figlerowicz M, Mozer-Lisewska I. Early virological response in children with chronic hepatitis C treated with pegylated interferon and ribavirin. *Infection* 2007; **35**: 175-179. [DOI: 10.1007/s15010-007-6072-5]
9. Echeverria N, Moratorio G, Cristina J, Moreno P. Hepatitis C virus genetic variability and evolution. *World J Hepatol* 2015; **7**(6): 831-845. [PMID: 25937861]; [PMCID: PMC4411526]; [DOI: 10.4254/wjh.v7.i6.831]
10. Abe S, Tabaru A, Ono M, Tai M, Narita R, Moriyama A, Otsuki M. High-dose interferon- $\alpha$  therapy lowers the levels of serum fibrogenesis markers over 5 years in chronic hepatitis C. *Hepatology Research* 2003; **25**: 22-31. [PMID: 12644035]
11. Chen Yi, Mei SLG, Thompson AJ, Christensen B, Cunningham G, McDonald L, Bell S, Iser D, Nguyen T, Desmond PV. Sustained virological response halts fibrosis progression: A long-term follow-up study of people with chronic hepatitis C infection. *PLoS One* 2017; **12**(10): e0185609. [PMID: 29065124]; [PMCID: PMC5655473]; [DOI: 10.1371/journal.pone.0185609]
12. Uojima H, Murakami S, Nakatani S, Hidaka H, Takeuchi A, Tanaka Y, Inoue T, Yamane K, Kubota K, Nakazawa T, Shibuya A, Tanaka Y, Koizumi W. Late Relapse after a Sustained Virological Response at 24 Weeks after Treatment with Daclatasvir and Asunaprevir Combination Therapy for Chronic Hepatitis C Virus Genotype 1b Infection with Liver Cirrhosis. *Internal Medicine* 2018; **57**(7): 951-956. [PMID: 29225269]; [PMCID: PMC5919851]; [DOI: 10.2169/internalmedicine.9671-17]
13. Salas-Villalobos TB, Lozano-Sepúlveda SA, Rincón-Sánchez AR, Govea-Salas M, Rivas-Estilla AM. Mechanisms involved in liver damage resolution after hepatitis C virus clearance. *Medicina Universitaria* 2017; **19**(75): 100-10. [DOI: 10.1016/j.rmu.2017.05.005]
14. Matsuura, K., Tanaka, Y. Host genetic variations associated with disease progression in chronic hepatitis C virus infection. *Hepatology Research* 2017; **48**(2): 127-133. [DOI: 10.1111/hepr.13042]
15. Li DK, Ren Y, Fierer DS, Rutledge S, Shaikh OS, Lo Re V 3rd, Simon T, Abou-Samra AB, Chung RT, Butt AA. The short-term incidence of hepatocellular carcinoma is not increased after hepatitis C treatment with direct-acting antivirals: An ARCHIVES study. *Hepatology* 2018; **67**(6): 2244-2253. [PMID: 29205416]; [DOI: 10.1002/hep.29707]
16. Innes H, Barclay ST, Hayes PC, Fraser A, et al. The risk of hepatocellular carcinoma in cirrhotic patients with hepatitis C and sustained viral response: role of the treatment regimen. *J Hepatology* 2018; **68**(4): 646-654. [PMID: 29155019]; [DOI: 10.1016/j.jhep.2017.10.033]
17. Mettke F, Schlevogt B, Deterding K, Wranke A, Smith A, Port K, Manns MP, Vogel A, Cornberg M, Wedemeyer H. Interferon-free therapy of chronic hepatitis C with direct-acting antivirals does not change the short-term risk for de novo hepatocellular carcinoma in patients with liver cirrhosis. *Aliment Pharmacol Ther* 2018; **47**(4): 516-525. [PMID: 29205405]; [DOI: 10.1111/apt.14427]