

**COMPARISON OF ADHERENCE AND PREVALENCE OF DEPRESSION AMONG HEPATITIS C INFECTED CIRRHOTIC AND NON-CIRRHOTIC PATIENTS TREATED WITH PEGYLATED INTERFERON PLUS RIBAVIRIN VERSUS DIRECT-ACTING ANTIVIRALS****Aikaterini Oikonomou\*<sup>1</sup>, Konstantinos Giakoumidakis<sup>1</sup>, Nikolaos V. Fotos<sup>1</sup>, Theodoros Androutsakos<sup>2</sup>, Ioannis Elefsiniotis<sup>1</sup> and Hero Brokalaki<sup>1</sup>**<sup>1</sup>Department of Nursing, School of Health Sciences, National and Kapodistrian University of Athens, 123 Papadiamantopoulou Ioanni Street, Goudi, Athens, 11527, Greece.<sup>2</sup>Department of Pathophysiology, "Laiko" General Hospital of Athens, 17 Agiou Thoma Street, Goudi, Athens, 11527, Greece.**\*Corresponding Author: Dr. Aikaterini Oikonomou**

Department of Nursing, School of Health Sciences, National and Kapodistrian University of Athens, 123 Papadiamantopoulou Ioanni Street, Goudi, Athens, 11527, Greece.

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**ABSTRACT**

**Background:** Adherence of hepatitis C infected patients to combination therapy of pegylated interferon (PEG-IFN) and ribavirin (RBV) is often inadequate. The, new, all-oral, direct-acting antivirals (DAAs) are expected to exhibit a better adherence profile due to a less complex administration schedule and fewer side effects, including depression. **Methods:** One hundred and twenty patients with chronic hepatitis C were included in the study. Sixty patients received PEG-IFN plus RBV (Group A) while the remaining sixty patients were treated with DAAs (Group B). Comparison of adherence and prevalence of depression were carried out between the two groups. Additionally, subgroup comparison of adherence and prevalence of depression were conducted between 21 cirrhotic patients from group A and 25 patients with cirrhosis from group B. Patient adherence was estimated with the «A-14 scale» and the prevalence of depression with «Beck Depression Inventory». **Results:** Patients from group A were found to be less compliant, with higher rates of clinical depression compared to patients from group B (45/60 vs 57/60,  $p=0.0039$  and 37/60 vs 13/60,  $p<0.0001$  respectively). Similarly, HCV-infected cirrhotic patients receiving PEG-IFN and ribavirin were less adherent with higher prevalence of depression compared to HCV-infected cirrhotic patients treated with DAAs (14/21 vs 24/25,  $p=0.0161$  and 15/21 vs 8/25,  $p=0.0169$  respectively). **Conclusion:** Treatment with DAAs seems to be associated with higher adherence rates and lower rates of depression compared to IFN-based treatment (PEG-IFN plus RBV) in both cirrhotic and non-cirrhotic patients. Consequently, DAAs could help to improve treatment efficacy and quality of life.

**KEYWORDS:** depression, direct-acting antivirals, patient adherence, pegylated interferon, ribavirin.**INTRODUCTION**

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide. The hepatic injury can range from minimal histological changes to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma, liver failure and death.<sup>[1,2]</sup> A sustained virologic response (SVR) is defined as undetectable HCV-RNA 12 or 24 weeks after treatment completion. Nearly 99% of the patients with chronic hepatitis C (CHC) are cured from infection when they achieve SVR.<sup>[3,4]</sup> The former standard of care for the treatment of CHC consisted of the combination of pegylated interferon (PEG-IFN) plus oral ribavirin (RBV).<sup>[5]</sup> However, the landscape of treatment for HCV infection has evolved substantially since the introduction of direct-acting antiviral agents (DAAs) that target viral proteins.<sup>[1,6]</sup> DAA-based regimens have substantially

reduced treatment length and have led to higher efficiency rates [more than 90% instead of 45-75% with the PEG-IFN plus RBV treatment (IFN-based treatment), depending on HCV genotype and liver fibrosis]. DAAs have also a better side effects profile, since they lack side effects like nausea/vomiting, depression, sleep problems, headaches, fatigue and flu-like symptoms and a less complex administration schedule.<sup>[7,8]</sup>

The World Health Organization defines treatment adherence as "the extent to which a person's behavior corresponds with agreed-upon recommendations from a health-care provider".<sup>[9]</sup> More specifically, medication adherence is defined as the patient's conformance with the provider's recommendation with respect to timing, dosage, and frequency of medication-taking during the prescribed length of time in order to produce a

therapeutic result. Unfortunately, approximately 20-30% of all medication prescriptions are not filled consistently, and nearly 50% of medications prescribed for chronic illnesses are not taken as prescribed. Published research on PEG-IFN plus RBV treatment regimens for HCV indicated that treatment response was directly affected by how closely the medication regimen was followed with cure being most likely when at least 85% adherence to the medication regimen was achieved. Published literature on adherence to interferon-based treatment regimens point to several facilitative factors, including: the absence of pre-existing psychiatric disorder, early detection, more than 12 years of education, successful follow-up appointments and at least a one-month period of total abstinence from substances (alcohol and drug use) prior to treatment initiation.<sup>[7,10]</sup> Especially depression seems to be the most common psychiatric side effect of PEG-IFN plus RBV treatment, with a prevalence ranging from 30% to 70%.<sup>[11]</sup> Studies focusing on the rate of SVR and factors associated with it show that severe depression leading to suicide ideation/suicide attempt is the main reason for early termination of antiviral treatment in CHC patients. Depressive symptoms occur mostly in the early stages of treatment and reach a peak between 4 and 16 weeks.<sup>[11]</sup>

Keeping in mind that the, new, all-oral, short-term, treatment with DAAs is simple and with no serious side effects one would expect better adherence from HCV-infected patients. The aim of this study was to compare the adherence and prevalence of depression among hepatitis C infected cirrhotic and non-cirrhotic patients treated with PEG-IFN plus RBV versus DAA-based regimens.

## MATERIALS AND METHODS

### Study Design and Sample

This was a cross-sectional study. HCV-infected patients treated with either PEG-IFN plus RBV or DAAs were initially screened and enrolled by convenience sampling at the Hepatology Outpatient Department of a general hospital in Athens, Greece from January 2016 to September 2018, in order to form the two comparative groups.

The inclusion criteria of patients were as follows: 1) diagnosed chronic hepatitis C of all genotypes, 2) anti-HCV treatment of at least one month's duration, 4) age  $\geq 18$  years, 5) adequate knowledge of the Greek language, 6) informed written consent of participation to the study.

The exclusion criteria of the study were the following: 1) known cognitive deficits, disturbances of memory and neurological diseases, 2) known cancer with bad prognosis, 3) psychiatric diseases, 4) active drug and alcohol use during the last month, 5) cirrhosis class C according to the Child-Pugh score, 6) HIV coinfection, 7) end stage chronic renal failure, 8) Class II-IV

(according to New York Heart Association Functional Classification) heart failure.

HCV infection was defined as positive HCV serum RNA. Patients were regarded as cirrhotic according to physicians' diagnosis, either with Fibroscan or non-invasive biomarkers. Educational level was defined as follows: Low educational level was regarded as primary school education, middle as high school education and high as university education.

Patients recruited in the study were initially divided in 2 groups: Group A with HCV infected patients receiving IFN-based treatment and group B receiving DAA-based regimens, matched according to gender, age, education level and HCV genotype. A statistical analysis and comparison of adherence and prevalence of depression was carried out between the two groups. Additionally, subgroup analysis and comparison of adherence and prevalence of depression was conducted between patients with liver cirrhosis, receiving both regimens.

The study was approved by the Ethics and Deontology Committee of Nursing Department of National and Kapodistrian University of Athens (Protocol number: 974) and the Scientific Council of hospital (protocol number: 18310). An oral permission was also given by the head physician and the head nurse of the hepatology department who were informed of the nature and purpose of the study. Full confidentiality and anonymity were maintained and the investigation was carried out in accordance with the Helsinki Declaration of 1975, as revised in 2013. Written informed consent was obtained from all individual participants included in the study.

### Instruments and Data Collection

Patients' adherence to medical treatment was estimated with A-14 scale and clinical depression with the Beck's Depression Inventory (BDI)<sup>[12, 13]</sup>. As defined by stratification of these scales, any patient with a total A-14 score  $\geq 50$  was classified as adherent to medical treatment while any patient with Beck's score  $\geq 10$  (traditional cutoff) was classified as having mild-severe clinical depression<sup>[12-15]</sup>. The proportion of adherent and depressive patients was used for comparison between the two groups.

A-14 scale was developed in 2009 by Jank *et al*<sup>[13]</sup> and is intended to describe the degree of adherence and the individual barriers that contribute to non-observance of pharmaceutical interventions. It includes 14 questions aimed at recording the factors that are poorly attached to treatment and is classified into the following categories: Invalid non-admission due to amnesia, subjective dose modification by the patient for safety and efficacy reasons, non-adherence to practical obstacles to day-to-day action such as cost and time consuming treatment and non-adherence to a negative view of drugs. The scoring of the answers was done with a four-point Likert type scale from "never" (4 points) to "very often." (0

points). The overall score ranges from 0 to 56. According to their score, patients are classified into non-adherent (score <50) or adherent (score 50-56, estimated adherence of at least 90%).

The A-14 scale is a reliable and valid tool (Cronbach  $\alpha = 0.861$ ), as well as a non-specific questionnaire for assessing drug addiction.<sup>[15]</sup> In Greece, it has not been used and therefore the permission was requested by W. E. Haefeli and translated into Greek according to the Brislin's model (Brislin, 1970).<sup>[13]</sup>

The Greek language adapted version of the BDI was used to screen for depression in HCV-infected patients. This scale consists of 21 structured questions presented in the form of multiple options. Each of the 21 questions is designed to approach a specific symptom or behavior that tends to occur in depressed patients, according to the DSM-IV diagnostic criteria. In particular, the scales measured are: sadness, despair, past failures, anecdote, guilt, self-esteem, self-cognition, suicidal thoughts, crying, mental stimulation, insomnia, irritability, decreased appetite, decreased concentration, fatigue, non-existence of sexual mood. Each question includes a series of four personal evaluation responses, which reflect the symptom intensity level and which are rated with 0 (minimum intensity), 1, 2 and 3 (maximum intensity). Adding the values of all 21 questions takes the total score of the person, which corresponds to different levels of depression. Any patient with Beck's score  $\geq 10$  (traditional cutoff) was classified as having mild-severe clinical depression<sup>[10,12,13,14]</sup>

Patients completed the questionnaires in a room isolated from the other patients. The researcher came into contact with patients and explained the purpose and the process of conducting the study, obtaining their written consent. Through a structured interview, the demographic and clinical data collection form was completed. The participant was then informed of the type of questionnaires, and was given the opportunity to ask questions. Data were collected by the same researcher each time, aiming to ensure the reliability and validity of the data collection process.

### Statistical Analysis

2x2 contingency tables for categorical data were analyzed with Fisher's exact test and unpaired t test was applied for the comparison of continuous variables. Shapiro-Wilk test was used as normality test for continuous variables. Statistical significance level was set to  $p=0.05$ . All statistics were conducted using the GraphPad Prism version 7.0 software package.

## RESULTS

### Demographic Characteristics and Clinical Data

*Characteristics of HCV-Infected Patients Participating in the Study.*

Initially a total matched number of 144 patients diagnosed with HCV-infection were identified. Twenty-four of these patients did not meet the inclusion criteria and therefore, were excluded from the study. Specifically, six patients had a psychiatric disease and two patients were under 18 years old while four other patients did not sign the written informed consent for participation to the study.

Finally, 120 matched patients treated for HCV infection were recruited in the study. Sixty HCV-infected patients who received PEG-IFN plus RBV (group A) were included in the study and were matched according to gender, age, education level and HCV genotype, with sixty HCV-infected patients who were treated with DAA-based regimens (group B): ombitasvir/paritaprevir/ritonavir and/or dasabuvir; sofosbuvir and daclatasvir; elbasvir and grazoprevir; velpatasvir and sofosbuvir; sofosbuvir and simeprevir; ledipasvir and sofosbuvir (Table 1). In all regimens RBV was added according to national guidelines. Treatment duration ranged from 8 to 48 weeks.

**Table 1: DAA-based regimens used.**

Regimen Used	Number of Patients
Led/Sof	8
Led/Sof + RBV	1
Omb/Par/Rit	7
Omb/Par/Rit + Das	4
Omb/Par/Rit + Das + RBV	6
Sof/Dac	3
Sof/Dac + RBV	5
Sof/Sim	1
Elb/Gra	11
Sof/Vel	6
Sof/Vel + RBV	8

**DAA:** Direct-Acting Antivirals; **Led/Sof:** Ledipasvir/Sofosbuvir; **Omb/Par/Rit:** Ombitasvir/Paitaprevir/Ritonavir; **Das:** Dasabuvir; **Sof:** Sofosbuvir; **Dac:** Daclatasvir; **Sim:** Simeprevir; **Elb:** Elbasvir; **Gra:** Grazoprevir; **Vel:** Velpatasvir; **RBV:** Ribavirin

Thirty-five males (58.3%) and 25 females with a mean age of 42.32 years were included in group A, with 33 males (55%) and 27 females with a mean age of 44.92 years being included in group B (Table 2,  $p=0.163$ ). Twenty-two patients in group A and 17 patients in group B had received high education. HCV genotypes 1b and 3 were the most common in both groups. Baseline characteristics of the patients included in the study are found in Table 2.

*Comparison of Adherence and Prevalence of Clinical Depression Among HCV-Infected Patients Receiving IFN-Based Treatment vs DAA-Based Regimens.*

Forty five of 60 HCV-infected patients from group A (75%) receiving PEG-IFN plus RBV vs 57 of 60 from group B (95%) treated with DAA-based regimens, were

found to be adherent to medical treatment (Table 2,  $p=0.0039$ ). Similarly, 37 of 60 HCV patients from group A (61.6%) receiving PEG-IFN plus RBV therapy vs 13

of 60 from group B (21.6%) treated with DAAs, were found to suffer from mild-severe depression (Table 2,  $p<0.0001$ ).

**Table 2: Characteristics of HCV-infected patients.**

		<b>Group A (IFN-based regimen, 60 patients) N (%)</b>	<b>Group B (DAA-based regimens, 60 patients) N (%)</b>	<b>p-value</b>
<b>Gender</b>	Male	35 (58.3)	33 (55.0)	0.854
	Female	25 (41.7)	27 (45.0)	0.854
<b>Age (mean <math>\pm</math> SD)</b>		42.32 $\pm$ 11.47	44.92 $\pm$ 8.61	0.163
<b>Educational level</b>	Low	8 (13.3)	11 (18.3)	0.6179
	Middle	30 (50.0)	32 (53.3)	0.8552
	High	22 (36.7)	17 (28.4)	0.4358
<b>Genotype</b>	Genotype 1a	8 (13.3)	10 (16.6)	0.7989
	Genotype 1b	22 (36.7)	24 (40.0)	0.8512
	Genotype 2	2 (3.3)	0 (0.0)	0.4958
	Genotype 3	20 (33.4)	17 (28.4)	0.6929
	Genotype 4	8 (13.3)	9 (15.0)	>0.9999
<b>Cirrhotic</b>		21 (35.0)	25 (41.6)	0.5735
<b>A-14 scale</b>	Adherence	45 (75.0)	57 (95.0)	<b>0.0039</b>
<b>Beck's scale</b>	Mild-severe depression	37 (61.6)	13 (21.6)	<b>&lt;0.0001</b>

INF, Interferon DAA, Direct-acting antivirals SD, Standard Deviation

*Subgroup Analysis of HCV-Infected Cirrhotic Patients Treated with Both Regimens.*

*Characteristics of HCV-Infected Cirrhotic Patients Participating in the Study.*

Twenty-one of 60 patients from group A (35%) had liver cirrhosis (group C) compared to 25 of 60 HCV-infected cirrhotic patients from group B (41.6%), (group D) ( $p=0.57$ ). The mean age of group C was 48.14 years and of group D 48 years (Table 3,  $p=0.96$ ). Group C included 8 males (38.1%) and 13 females while group D included 12 males (48%) and 13 females (Table 3). Similarly, there was no statistically significant difference between the two groups with respect to educational level and HCV genotype (Table 3).

*Comparison of Adherence and Prevalence of Clinical Depression Among HCV-Infected Cirrhotic Patients Receiving IFN-Based Treatment vs DAA-Based Regimens.*

Fourteen of 21 HCV-infected cirrhotic patients from group C (66.7%) vs 24 of 25 patients from group D (96%), were found to be adherent to medical treatment (Table 3,  $p=0.016$ ). Similarly, 15 of 21 HCV-infected patients with cirrhosis from group C (71.4%) vs 8 of 25 from group D (32%) were found to suffer from mild-severe depression (Table 3,  $p=0.0169$ ).

**Table 3. Characteristics of HCV-infected cirrhotic patients.**

		<b>Group C (IFN-based regimen, 21 patients) N (%)</b>	<b>Group D (DAA-based regimens, 25 patients) N (%)</b>	<b>p-value</b>
<b>Gender</b>	Male	8 (38.1)	12 (48)	0.5608
	Female	13 (61.9)	13 (52)	0.5608
<b>Age (mean <math>\pm</math> SD)</b>		48.14 $\pm$ 10.12	48.0 $\pm$ 9.09	0.96
<b>Educational level</b>	Low	3 (14.3)	2 (8.0)	0.6476
	Middle	13 (61.9)	15 (60.0)	>0.9999
	High	5 (23.8)	8 (32.0)	0.7437
<b>Genotype</b>	Genotype 1a	2 (9.5)	4 (16.0)	-
	Genotype 1b	10 (47.6)	11 (44.0)	-
	Genotype 2	1 (4.8)	0 (0.0)	-
	Genotype 3	5 (23.8)	6 (24.0)	-
	Genotype 4	3 (14.3)	4 (16.0)	-
<b>A-14 scale</b>	Adherence	14 (66.7)	24 (96.0)	<b>0.0161</b>
<b>Beck's scale</b>	Mild-severe depression	15 (71.4)	8 (32.0)	<b>0.0169</b>

INF, Interferon DAA, Direct-acting antiviral SD, Standard Deviation

## DISCUSSION

Apart from drugs used, adherence to treatment is an important step in treating chronic infections. The complexity of given regimens and possible side effects make adherence to treatment even more difficult, leading sometimes to treatment failure. We conducted a study in both cirrhotic and non-cirrhotic HCV-infected patients trying to figure out if treatment with DAAs can lead to patients' greater adherence and lower incidence of treatment related depression.

In our study, the proportion of adherent patients receiving treatment with PEG-IFN and RBV was found to be statistically significantly lower compared to patients treated with DAAs. Furthermore, patients treated with DAAs displayed lower prevalence of depression. Both findings were independent from gender, age, educational level and HCV genotype. Furthermore, when subgroup analysis of cirrhotic HCV-infected patients, was performed, adherence to treatment was better with the DAAs compared to PEG-IFN and ribavirin regimen, while depression found more often to the patients using the latter drugs.

These findings confirm previous studies indicating that both cirrhotic and non-cirrhotic patients are less adherent to treatment regimens associated with significant psychiatric side effects such as depression.<sup>[16-20]</sup> Other studies have found that treatment-naïve patients are less likely to be adherent to treatments with IFN and/or RBV due to their inability to cope with the side effects such as fatigue or depression, especially if treatment is prolonged.<sup>[21,22]</sup> Findings such as these have important clinical implications, as RBV-containing regimens may remain the preferred treatment for the most difficult to treat patients, such as those who are treatment-experienced with advanced fibrosis.

Consistent with our findings, previous studies support that the actual rate of adherence with the IFN-free regimen is very high ( $\geq 95\%$ ),<sup>[10,23]</sup> which continues to attest to the superiority of such regimens. Our study supports the fact that DAAs were associated with better adherence even in the difficult to treat cirrhotic HCV subgroup. Although, DAA-based regimens are characterized by limited side effects and high treatment efficacy<sup>[10]</sup>, it is important to note that adherence is clinically significant, since, regardless of the regimen used, nonadherence leads to lower SVR rates. This indicates that even in the era of DAAs, adherence will remain of utmost importance.<sup>[10]</sup>

This study's generalizability is limited by its relatively small sample size and its heterogeneity (different stage of disease, treatment regimen etc.). Another limitation is the fact that, we could not assess the impact of adherence and SVR to health-related quality of life (HRQL) after treatment cessation due to lack of follow-up. Moreover,

difficult to treat HCV subpopulations, such as patients with renal failure, decompensated cirrhosis class C according to the child-Pugh score or liver transplants, were not included in the study. Finally, a number of socio-economic and clinical factors which may also interfere with adherence and therefore HRQL, including residence, social support, route of HCV transmission, duration of infection, major comorbidities, etc., were not taken into account, affecting generalizability.<sup>[1, 3,7, 24]</sup>

## CONCLUSION

To conclude, in our study, HCV-infected patients treated with DAA-based regimens, were associated with excellent adherence and less prevalence of clinical depression for both cirrhotic and non-cirrhotic HCV patients. Better adherence to medications and limited psychiatric side effects, such as depression, are expected to improve health-related quality of life during treatment and therefore lead to better clinical outcomes. Ongoing assessment of adherence, efficacy and comparative effectiveness of these treatments is a crucial area of future research for patients with chronic HCV infection.<sup>[6]</sup>

## ABBREVIATIONS

HCV: Hepatitis C virus  
SVR: Sustained virologic response  
CHC: Chronic hepatitis C  
PEG-INF: Pegylated Interferon  
RBV: Ribavirin  
DAA: Direct-acting antiviral  
HRQL: Health related quality of life

## CONFLICTS OF INTEREST DISCLOSURE

Authors have no conflict of interest to disclose.

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