


BRIEF COMMUNICATION

Incidence of depression in patients with hepatitis C treated with direct-acting antivirals

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Objective: Depression has been associated with hepatitis C, as well as with its treatment with proinflammatory cytokines (i.e., interferon). The new direct-acting antiviral agents (DAAs) have minimal adverse effects and high potency, with a direct inhibitory effect on non-structural viral proteins. We studied the incidence and associated factors of depression in a real-life prospective cohort of chronic hepatitis C patients treated with the new DAAs.

Methods: The sample was recruited from a cohort of 91 patients with hepatitis C, of both sexes, with advanced level of fibrosis and no HIV coinfection, consecutively enrolled during a 6-month period for DAA treatment; those euthymic at baseline (n=54) were selected. All were evaluated through the depression module of the Patient Health Questionnaire (PHQ-9-DSM-IV), at three time points: baseline, 4 weeks, and end-of-treatment.

Results: The cumulative incidence (95%CI) of major depression and any depressive disorder during DAA treatment was 13% (6.4-24.4) and 46.3% (33.7-59.4), respectively. No differences were observed between those patients with and without cirrhosis or ribavirin treatment ($p > 0.05$). Risk factors for incident major depression during DAA treatment included family depression (relative risk 9.1 [1.62-51.1]), substance use disorder (11.0 [1.7-73.5]), and baseline PHQ-9 score (2.1 [1.1-3.1]).

Conclusions: The findings of this study highlight the importance of screening for new depression among patients receiving new DAAs, and identify potential associated risk factors.

Keywords: Depression; direct-acting antivirals; DAA; hepatitis C; PHQ-9

Introduction

Depression is a common mental illness¹ and a leading cause of disability worldwide. Chronic exposure to hepatitis C virus (HCV) and previous antiviral treatment with interferon alpha has been associated with major depression.^{2,3} HCV infection leads to chronic hepatitis C (CHC) in around 80% of cases, and, if untreated, progresses to liver cirrhosis in one in five patients within 20 to 50 years after initial infection; of these, 5 to 10% will develop hepatocellular carcinoma or decompensated liver disease.⁴ CHC has been recognized as a systemic disease with many extrahepatic manifestations, including feelings of depression, anhedonia, fatigue, irritability, anxiety, insomnia, and increased sensitivity to pain.⁵ There is some evidence of direct neuroinvasion by HCV,⁶ as well as of a chronic, systemic immune activation.⁷

Interactions of these factors with several neurobiological pathways, neurotransmission, and neurotrophic mechanisms may account for the pathogenesis of neuropsychiatric symptoms in CHC.^{8,9}

Until a few years ago, antiviral treatment for CHC involved a weekly injection of pegylated interferon-alpha (IFNa), a proinflammatory cytokine, together with daily weight-based doses of ribavirin (RBV) for 24 to 48 weeks. This regimen was known to cause major depression in around 30% of patients,³ beside a wide range of other adverse events (AEs), with a high rate of treatment discontinuation¹⁰ and additional effects on physical and mental health-related quality of life.¹¹ Increased understanding of the HCV viral cycle in the last decade led to the development of direct-acting antiviral agents (DAA) that have minimal AEs and high potency, with a direct inhibitory effect on non-structural viral proteins.¹² The sustained

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virological response rate with DAA therapy is over 95% in most patients. With the use of all-oral DAA combinations, the short- and long-term prognosis for HCV-infected patients has improved significantly.¹³

The aims of this study were to evaluate the incidence of and risk factors associated with depressive disorders during DAA treatment in a real-life, prospective cohort of patients with CHC with advanced liver disease.

Methods

Patients

All consecutive patients with HCV mono-infection starting all-oral DAA therapy at the Liver Unit of Hospital Clínic de Barcelona (Spain), University of Barcelona, from June to December 2015 were considered for the study. Patients with HIV coinfection were not considered for this study, as they are treated at the Infectious Diseases Unit. From this initial cohort of patients, we selected those who were euthymic at baseline to evaluate the incidence of depression during DAA treatment.

All patients provided written informed consent for participation. The study protocol was approved by the institutional research ethics committee.

Demographic, clinical, and virological data at baseline, were collected. Family and personal history of depression and alcohol/drug use disorder (SUD) were also recorded. All participants were clinically assessed at three points: baseline, at 4 weeks (4W) of DAA therapy, and at the end of treatment (EOT).

Liver fibrosis was assessed at baseline by means of transient elastography (TE). Liver stiffness ≤ 7.8 kilopascals (kPa) was defined as F_{0-1} ; 7.8-9.4 kPa, as F_2 ; 9.5-13.9 kPa, as F_3 ; and ≥ 14 kPa, as F_4 or cirrhosis. Cirrhosis could also be diagnosed by other methods: liver biopsy, clinical evidence (i.e., gastroesophageal varices), and/or the presence of ultrasonographic criteria. Patients with cirrhosis were screened for hepatocellular carcinoma every 6 months as per clinical practice.

Antiviral treatment

DAA regimen, duration of therapy (12 or 24 weeks), and use of concomitant ribavirin (RBV) were planned at the discretion of the treating physician, in accordance with national and international recommendations at that time.¹² At the time of the study, access to all-oral IFN-free DAA therapy in Spain was restricted to patients with advanced liver disease (F_3 or cirrhosis) or those with mild liver disease (F_{0-2}) but concomitant extrahepatic manifestations. Viral eradication or sustained virological response (SVR) was defined as undetectable viremia (HCV-RNA) at 12 weeks after the end of treatment (12AT).

Clinical assessment

All enrolled patients were screened for the presence of current depressive symptoms by means of the Spanish-validated version of the self-administered PHQ-9 questionnaire for CHC patients.¹⁴ The items on the PHQ-9

correspond to the symptom criteria for depressive disorders as outlined in the DSM-IV.¹⁵ The depression module (PHQ-9) comprises nine items rated from 0 to 3 (not at all, several days, more than 50% of days, and nearly every day). Major depression is diagnosed if patients score 2 or 3 on five or more symptom criteria in the past 2 weeks, and if one of the symptoms is depressed mood or anhedonia. Other depression is diagnosed if two, three, or four depressive symptoms have been present in the last 2 weeks and if one of the symptoms is depressed mood or anhedonia. This questionnaire has shown good psychometric properties.¹⁴ The PHQ-9 was administered before each medical visit and blinded to virological results.

Patients with depressive disorders were referred to an independent senior psychiatrist and treated as necessary.

Statistical analysis

The baseline characteristics of patients in the sample are presented as mean (standard deviation) for numerical variables and as absolute and relative frequencies for categorical variables. The cumulative incidence of major depression and any depression disorder (i.e., both major depression and other depressive disorder) during DAA treatment was estimated and 95% confidence intervals (95%CI) were calculated. Logistic binomial regression models were fitted to study possible risk factors for the incidence of major depression and any depression. An effect-size measure of these models, relative risk (RR), was estimated with 95%CIs.

Statistical analyses were carried out using the R free software environment for statistical computing (The R Foundation for Statistical Computing; Vienna, Austria), version 3.4.2. Statistical significance was set at $p = 0.05$.

Results

Sample selection

During the 6-month study period (June to December 2015), 93 subjects were selected before starting antiviral therapy, all of whom agreed to participate. One patient did not start antiviral treatment, and another patient did not complete the clinical assessment; thus, neither was included. Of the 91 patients starting DAA treatment, 54 (59.3%) were euthymic at baseline and thus eligible for inclusion. Table 1 shows their baseline characteristics.

Of the 54 patients who were euthymic at baseline, 46 (85.2%) received DAA treatment (sofosbuvir; ledipasvir; 2D/3D paritaprevir/ombitasvir/ritonavir with or without dasabuvir; or daclatasvir) for 12 weeks, and 8 (14.8%) were treated for 24 weeks. Thirty-nine (72%) received concomitant treatment with RBV. All patients achieved SVR (100%) after DAA treatment, confirmed at 12AT.

Incidence of depression

Figure 1 shows the cumulative incidence of depression measured by PHQ-9 during antiviral treatment (at 4 weeks

Table 1 Characteristics of the euthymic cohort (n=54) of hepatitis C patients before DAA treatment

	All sample (n=54)	Euthymic during DAA (n=29)	Incident depression (any)* during DAA (n=25)	Incident major depression† during DAA (n=7)
Sociodemographic and HCV variables				
Age, years	61.1 (12)	60.5 (12.1)	61.3 (12.2)	57.0 (16.2)
Gender (male)	28 (51.9)	13 (46.9)	15 (57.7)	4 (57.1)
HCV genotype				
1a	12 (22.2)	6 (20.7)	6 (24)	2 (28.6)
1b	37 (68.5)	22 (75.9)	15 (60)	3 (42.9)
2	1 (1.9)	0 (0)	1 (4)	0 (0)
3	3 (5.6)	1 (3.5)	2 (8)	1 (14.3)
4	1 (1.9)	0 (0)	1 (4)	1 (14.3)
Previous non-responders to PegIFN/RBV therapy	28 (51.9)	16 (55.2)	14 (56)	1 (14.3)
Liver stiffness \geq 21 kPa (n=51)	14 (27.5)	7 (25.9) [‡]	7 (29.2) [§]	2 (28.6)
Fibrosis stage by TE				
F ₀₋₁	4 (7.4)	2 (6.9)	2 (8)	0 (0)
F ₂	1 (1.9)	1 (3.5)	0 (0)	0 (0)
F ₃	11 (20.4)	6 (21.7)	5 (20)	3 (42.9)
F ₄	38 (70.4)	20 (68.9)	18 (72)	4 (57.1)
Previous decompensation of cirrhosis	10 (26.3)	6 (31.6)	4 (21.1)	1 (25.0)
Child-Pugh Score in cirrhosis (n=37)				
A (%)	29 (78.4)	13 (68.4)	16 (88.9)	4 (100)
B (%)	8 (21.6)	6 (31.6)	2 (11.1)	0 (0)
MELD score (n=32)				
< 10	20 (62.5)	9 (52.9)	11 (73.3)	3 (100)
\geq 10	12 (37.5)	8 (47.1)	4 (26.7)	0 (0)
Albumin (g/dL)	41.4 (4.7)	41.0 (4.8)	41.4 (5.0)	44.3 (1.9)
Platelets (10 ⁹ /mL)	127.9 (68.1)	128.9 (63.1)	124.7 (71.2)	147.4 (59.9)
Relevant comorbidity [¶]	54 (100)	29 (100)	25 (100)	7 (100)
Psychiatric variables				
Family history of depression	10 (18.5)	6 (21.4)	4 (15.4)	4 (57.1)**
Family history of SUD	6 (11.1)	3 (10.7)	3 (11.5)	3 (42.9)**
Personal history of depression	13 (24.1)	9 (32.1)	4 (15.4)	2 (28.6)
Personal history of SUD	5 (9.3)	3 (10.7)	2 (7.7)	2 (28.6)
PHQ-9 total score (0 to 27)	1.3 (1.4)	1.4 (1.4)	1.2 (1.4)	2.6 (1.4)**
Treatment variables				
DAA with RBV	39 (72.2)	20 (71.4)	19 (76.0)	6 (85.7)
DAA without RBV	15 (27.8)	9 (28.6)	6 (24.0)	1 (14.3)

Numerical variables given as mean (SD); categorical variables, as n (%).

DAA = direct-acting antivirals; F = fibrosis score; HCV = hepatitis C virus; IFN = interferon; kPa = kilopascals; MELD = model for end-stage liver disease; PHQ-9 = Patient Health Questionnaire, depression module; RBV = ribavirin; SD = standard deviation; SUD = substance use disorder; TE = transient elastography.

* Any depression is the sum of "other depression" (diagnosed if two, three, or four depressive symptoms have been present in the last 2 weeks and if one of the symptoms is depressed mood or anhedonia) and "major depression."

† "Major depression" is diagnosed if the patient has scored 2 (more than 50% of days) or 3 (nearly every day) on five or more DSM-IV symptom criteria in the past 2 weeks, and if one of the symptoms is depressed mood or anhedonia.

‡ n=27; § n=24; || n=7.

¶ Ischemic cardiovascular events and arrhythmias, current or previous history of neoplastic disease, cryoglobulinemic vasculitis, chronic obstructive pulmonary disorder (COPD), or any disease potentially impacting activities of daily living.

**p < 0.05.

and at end-of-treatment) among patients euthymic at baseline (n=54). The cumulative incidence was 12.9% (95%CI 6.4-24.4) (n=7) for major depression, and 46.3% (95%CI 33.7-59.4) (n=25) for any depression. Concerning cirrhosis and use of RBV during DAA treatment, the differences between groups for both major depression and any depression were not significant (p > 0.05).

Risk factors associated with depression during direct-acting antiviral treatment

Regarding major depression, univariate logistic binomial regression indicated a statistically significant association with family history of depression (RR = 9.1, 95%CI 1.6-51.1), family history of substance use disorder (RR = 11.0, 95%CI 1.7-73.5), and higher PHQ-9 baseline score

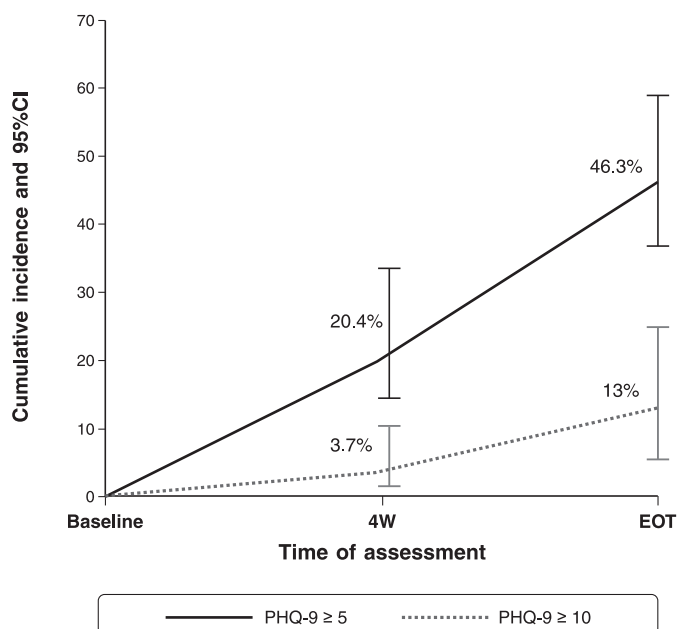


Figure 1 Cumulative incidence (95%CI) of major depression (red line) and any depression (blue line) during DAA treatment in patients euthymic at baseline (n=54). 95%CI = 95% confidence interval; PHQ-9 = Patient Health Questionnaire 9; PHQ-9 > 10 = major depression; PHQ-9 > 5 = any depressive disorder; 4W = 4 weeks of treatment; EOT = end of treatment (12 or 24 weeks).

(RR = 2.1, 95%CI 1.1-3.9, for every one-point increase in baseline score). No multivariate models were fitted for the incidence of depression because of the number of incident cases throughout the study (n=7/54). Concerning the development of any depression during DAA, no baseline characteristic was identified as a risk factor on univariate analysis.

Discussion

Several important findings were revealed in the present study. First, 13% of patients who were euthymic at baseline developed major depression during DAA treatment, and up to 40% developed depressive symptoms. Dual antiviral treatment based on IFN- α with RBV was associated with a high incidence of major depression (25-40%) in the past, mainly due to its IFN- α pro-inflammatory properties.^{3,16} As DAA works instead by direct inhibition of the various steps of HCV replication, a direct neuropsychiatric effect was not expected. Thus, other mechanisms might explain the incidence of depression observed. First, four in five patients included in our study received RBV, an antiviral co-agent with an unclear mechanism of action that is known to have negative effects on mental health.¹⁷ Nevertheless, it was not identified as a confounding factor when a specific analysis was performed. Second, the incidence of depression may be related to the advanced liver disease and medical comorbidity of this cohort, as these patients often experience more symptoms related to cirrhosis.^{18,19} However, when we controlled for the presence of cirrhosis, no statistically significant differences were found. Importantly, some

factors seem to be associated with a high relative risk of major depression during DAA treatment.

Second, CHC patients with a family history of depression before starting antiviral treatment had a more than fourfold increased risk of developing depression during DAA treatment. Moreover, every one-point increase in baseline PHQ-9 score was associated with a twofold risk (RR = 2.1) of incident depression during DAA treatment. Neither these factors nor others were associated with the incidence of mild depressive symptoms during DAA treatment. In the context of allostatic load, the subgroup of HCV patients with these risk factors may be more vulnerable to major depression.²⁰ Large naturalistic cohort studies would be needed to confirm these results.

This study is not free from limitations. Due to the sample size, the advanced stage of liver disease in the patients, their relevant comorbidities, and the absence of patients with HIV coinfection, any generalization of our results should be approached with caution. Because of the naturalistic cohort design, the study lacked a control group, and patients were included consecutively.

In conclusion, direct-acting antiviral treatment for chronic hepatitis C was associated with a lower incidence of major depressive episode than previous classical treatment with interferon-alpha. However, the results of this study highlight the importance of screening for depression, and its associated risk factors, over the course of DAA treatment.

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Disclosure

ZM has served as advisor for Gilead and has received speaker fees from AbbVie, Gilead, Jansen, and MSD. SL has served as advisor for Gilead, AbbVie, and MSD, and has received speaker fees from AbbVie, Gilead, Jansen, and MSD. XF has received unrestricted grant support from AbbVie and Gilead, and has served as advisor for AbbVie and Gilead. The other authors report no conflicts of interest.

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