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Letter to the editor

Impact of direct-acting antiviral drugs for chronic hepatitis C on mood: Preliminary results from a longitudinal study

Dear Editor,

Hepatitis C virus (HCV) infection has an epidemic, chronic course with a high risk of potentially lethal consequences, such as cirrhosis and hepatocellular carcinoma [1]. Treatment with interferon-alpha (IFN-α) determines the achievement of sustained virological response (SVR) in up to 60% of cases, and decreases overall mortality [2]. However, IFN-α increased the risk of a patient developing a major depressive episode (MDE) by up to 34.8% for observation times between 4 and 48 weeks [3].

Recently, new oral direct-acting antiviral drugs (DAAs) with antiprotease and antipolymerase activity, such as sofosbuvir, simeprevir, daclatasvir, velpatasvir, have proven safe and tolerable, and show high rates of efficacy [4]. However, at present, it is unknown whether they cause the same psychopathological complications as IFN-α. In this cohort study, the effects of a DAA protocol on psychological function were investigated during the first 8 weeks of the trial.

The study subjects comprised all patients referred to the Center for the Study of Liver Diseases at the University Hospital of Cagliari (Sardinia) from November 2015 to January 2018 and diagnosed with a chronic HCV infection that were eligible for DAA therapy. The study protocol was approved by the competent ethical committee (PG/2015/16964) and registered at ClinicalTrials.gov (Identifier: NCT03313154).

Two groups were compared: the treatment group, which received immediate treatment with DAAs (DAAs+), and a control group, in which subjects were entered into a waiting list for non-availability of treatment (DAAs−). A non-parametric Kaplan-Meier estimation with Cox proportional hazards model, both univariate and multivariate, including age (continuous) and sex (women as the referent group) as covariates, was used to calculate differences in survival between the DAAs+ and DAAs− groups. Survival was calculated against the negative event of being positive for MDE on the 9-item Patient's Health Questionnaire (PHQ-9) (threshold ≥10) [5]. Participants were censored if they did not convert to MDE after 8 weeks of the trial. In a sensitivity analysis, we assumed that people who left the trial early (dropouts) had a negative event.

Overall, 100 subjects were enrolled into this study (N = 50 in each group). The DAAs+ group included younger participants (57 ± 11 versus 64 ± 15 years of age; t = 2.51; df = 98; p = 0.014), with slightly lower baseline PHQ-9 scores (3.54 ± 4.16 versus 5.34 ± 4.51; t = −2.07; df = 98; p = 0.041).

Fifteen subjects in the DAAs− group and one subject in the DAAs+ group dropped out of the study. Eight subjects in the DAAs+ group (16%) and 13 subjects in the DAAs− group (26%) were positive for MDE, as determined by the PHQ-9 after 8 weeks of the study.

The occurrence of MDE, as measured by the PHQ-9, was no more likely in the DAAs+ group than in the DAAs− group, based on the Kaplan-Meier survival analysis (Fig. 1).

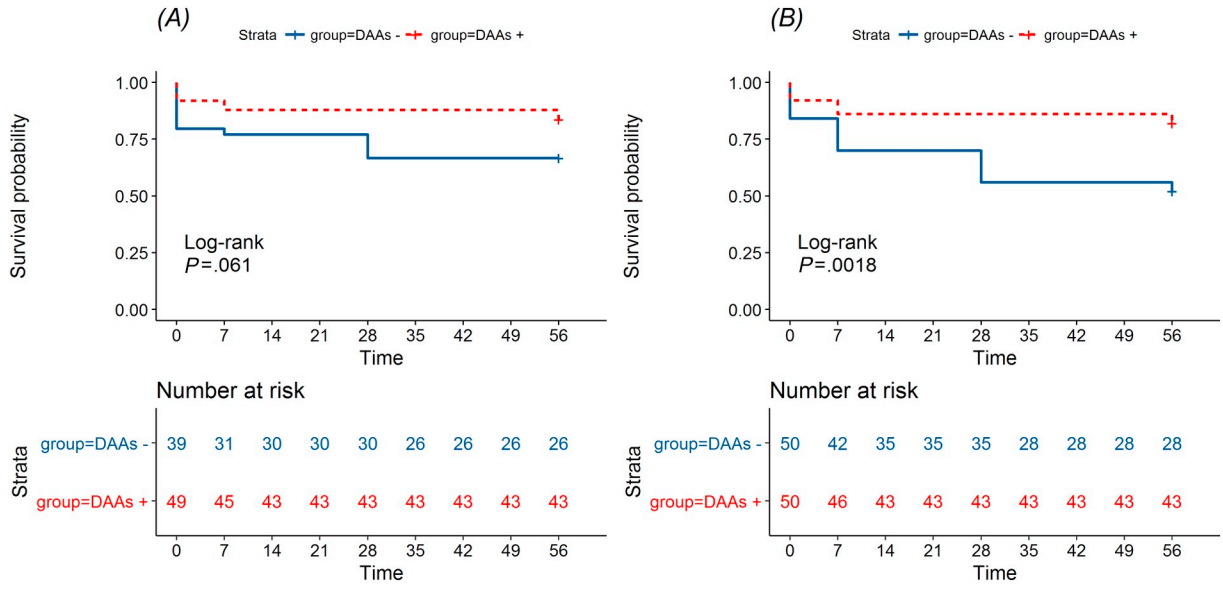

Fig. 1. Survival curves with number at risk by time based on Kaplan-Meier estimates of (A) negative event as representative of positivity for major depressive episode on the PHQ-9, and (B) as positivity for major depressive episode on the PHQ-9 or being a dropout. Time represents a 7-day interval.

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Table 1
Univariate and multivariate Cox proportional regression analyses of the primary endpoint.

	HR	95% CI	p-Value	Likelihood ratio	Schoenfeld Residuals Test
Major depressive episode on the PHQ-9					
Univariate					
DAAs+	0.43	0.18–1.05	0.064	LR = 3.54, p = 0.059	χ^2 = 0.25, p = 0.615
Multivariate					
DAAs+	0.47	0.19–1.16	0.101	LR = 4.30, p = 0.231	χ^2 = 0.11, p = 0.742
Sex	0.68	0.29–1.63	0.397		χ^2 = 0.12, p = 0.729
Age	1.00	0.97–1.03	0.851		χ^2 = 0.26, p = 0.607
Major depressive episode on the PHQ-9 and dropouts					
Univariate					
DAAs+	0.31	0.14–0.67	0.003	LR = 9.95, p = 0.0016	χ^2 = 0.66, p = 0.417
Multivariate					
DAAs+	0.33	0.15–0.73	0.0065	LR = 10.62, p = 0.014	χ^2 = 0.40, p = 0.527
Sex	0.75	0.37–1.50	0.416		χ^2 = 0.42, p = 0.516
Age	1.00	0.98–1.02	0.995		χ^2 = 0.07, p = 0.788

A Cox regression analysis confirmed that there was no greater risk for the development of MDE in the DAAs+ group than the DAAs− group, even when sex and age were accounted for. By including dropouts into the negative events, the DAAs+ group was less likely to be at risk for the development of MDE or dropout than the DAAs− group. No evidence against the proportionality assumption was found on the Schoenfeld Residuals Test (Table 1, Supplemental Material).

People with HCV infection are burdened by a high rate of mental disorders, principally in the spectrum of mood disorders [6]. Some psychopathologic symptoms present before the start of treatment are highly predictive of the onset of depressive disorder during IFN-α antiviral therapy [7,8], and govern the reduction of the dosage and the high rates of discontinuation of antiviral therapy [9]. Moreover, a high risk of depressive recurrence after the end of the therapy was recently shown among patients with chronic HCV-related hepatitis diagnosed with IFN-α-induced depression [10]. A careful psychiatric and neuropsychological assessment, before, during, and after antiviral treatment, should therefore be an indispensable part of HCV-related chronic hepatitis screening and therapy.

In this cohort study, a DAAs protocol showed no greater risk of depressive episode in people undergoing treatment, compared with a waiting list control group. These findings are compelling owing to the increased risk of depression during treatment with IFN-α: overall, DAAs may become the treatment of choice for people with HCV chronic hepatitis at a higher risk of developing depression.

However, owing to limitations of this study (i.e. small sample size, lack of randomization, exclusive reliance on self-report tools for the ascertainment of the case status, very low baseline PHQ-scores, and high number of dropouts in the control group), further study is needed to confirm our preliminary results.

Declaration of interest

None.

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