

# Depression and suicide ideation in chronic hepatitis C patients untreated and treated with interferon: prevalence, prevention, and treatment

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## Abstract

Interferon-based therapies were until recently the standard of care in chronic hepatitis C (CHC), despite their side effects. We aimed to review the available data on the depression and suicide in CHC patients receiving or not antiviral therapy based on interferon treatment. A PubMed search was performed, identifying relevant papers published between 1991 and January 2015 concerning major depressive disorders and suicidal risk in patients under interferon. A total of 21 relevant papers were retrieved. Prospective studies reported depression as the most common side effect of interferon, with an incidence peak between weeks 8 and 12 of therapy. Suicide risk was analyzed in 7 of the reviewed articles, and case reports of attempted suicide were discussed. Moreover, studies have shown that pretreatment with serotonin reuptake inhibitors is a good strategy for the prevention of interferon-induced depression.

**Keywords** Depression, antiviral therapy, pegylated interferon, ribavirin, suicide, chronic hepatitis C, neuropsychiatric events

*Ann Gastroenterol 2015; 28 (4): 440-447*

## Introduction

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide, affecting an estimated 170 million people [1,2]. Current standard of care for the treatment of chronic hepatitis C (CHC) infection was until recently represented by the combination of pegylated interferon  $\alpha$  (peg-IFN- $\alpha$ ) and ribavirin (RBV) for either 24 or 48 weeks depending on genotype. Until the approval of sofosbuvir, simeprevir and daclatasvir in 2014 as IFN-free regimens, even after the introduction in 2011 of the first generation direct acting antivirals, namely boceprevir and telaprevir, IFN was also used as a component of a triple combination regimen. However, by reasons regarding the costs of therapy, there are many countries worldwide where IFN therapy is still available as therapy for CHC, or patients still continuing the therapy. The primary goal of CHC therapy is sustained virological response (SVR), defined as

an undetectable HCV-RNA level (<50 IU/mL) 24 weeks after treatment withdrawal.

Although SVR is obtained in 46% of cases in patients infected with genotype 1, and, respectively 76% in patients infected with genotypes 2 and 3, the combination therapy with peg-IFN- $\alpha$  therapy and RBV is often discontinued because of significant neuropsychiatric adverse events which may limit its use. The most common psychiatric side effect is depression, with the prevalence ranging from 30% to 70% [2]; consequently, depending on the gravity of depressive disorder, psychosis, suicidal ideation, and suicide attempt may occur [3-5]. Studies focusing on the rate of SVR and factors associated with SVR show that severe depression leading to suicide ideation/suicide attempt is also the reason for early termination of antiviral treatment in CHC patients [6]. These data imply a proper management and prevention strategies of depression in these patients according to current guidelines. Depressive symptoms occur mostly in the early stages of treatment and reach a peak between 4 and 16 weeks [4].

Given the fact that there is an increased prevalence of psychiatric comorbidity in CHC patients compared to the general population [7], and that psychiatric disorders represent a contraindication to the antiviral therapy, an exhaustive review of the psychiatric side effects occurring during peg-IFN- $\alpha$  therapy is useful. Mental health issues may also reduce quality of life and interfere with treatment compliance.

In this paper we review the studies related to major depressive disorders and its most severe consequences suicide ideation and suicide attempts in CHC patients undergoing

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Conflict of Interest: None

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Received 5 October 2014; accepted 3 June 2015

antiviral treatment (peg-IFN- $\alpha$  in association with RBV), we present the main pathophysiological mechanisms of IFN- $\alpha$ -induced depression, and discuss prevention versus management strategies during and after cessation of IFN- $\alpha$  therapy. We also briefly report on the incidence of depression among untreated CHC patients, for better understanding of the effects of IFN-induced metabolic changes in the context of the already affected central nervous system in CHC patients. This information also serves as a “control” to the data on treated patients.

## Materials and methods

A PubMed search of all published articles on psychiatric adverse events of IFN- $\alpha$  therapy in CHC patients was carried out. We limited our search to articles published between 1991 (since IFN therapy for CHC had been first approved) and January 2015. We focused on articles concerning the topic of major depressive disorders and suicidal risk; the search included the terms: major depression, major depressive disorders, interferon alpha therapy, IFN alpha, CHC, suicide, suicide risk, suicide ideation. Only articles in English and French were included. The titles and abstracts were examined and after obtaining full-text articles of potentially relevant studies, inclusion and exclusion criteria were applied. We herein included prospective studies reporting the incidence of IFN- $\alpha$ -related major depressive disorders, suicide ideation, or suicide attempt; and observational studies estimating frequency of depression in CHC patients under IFN- $\alpha$  treatment.

We excluded studies regarding the onset of depression in CHC patients receiving antiviral treatment other than IFN- $\alpha$  (IFN-free regimens), other neuropsychiatric side effects than major depression (mood alteration, anxiety, cognitive impairment and somatic symptoms), and studies focusing on treatment and prevention of IFN- $\alpha$ -induced depressive disorders.

The majority of papers included in this review analyze the prevalence of major depressive disorder related to antiviral therapy (IFN- $\alpha$  monotherapy or in combination with RBV).

## Results

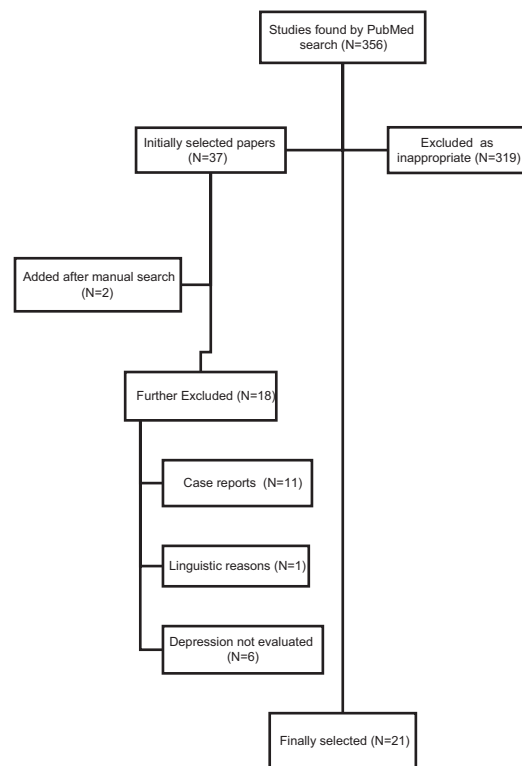
Using PubMed database, 356 articles were identified and titles and abstracts were examined. At this stage 319 were excluded because they did not meet the inclusion criteria. We further excluded 18 case reports and articles not serving the purpose of this paper. After we examined the references of remaining articles we obtained 21 relevant papers (Fig. 1). Selected articles were reviewed and we summarized in (Table 1) the following data: author, year of publication, number of patients included in the study, dose and type of IFN- $\alpha$ , and adjunctive RBV, duration of antiviral treatment, incidence of major depressive disorder and suicide ideation/suicide attempts when reported, scales and methods of assessment of depression, and risk factors for depression.

## Depression and suicide risk in untreated CHC patients

Psychiatric disorders are reported to be frequently associated in patients with CHC and HIV infection [7]. Psychiatric comorbidities are also more commonly reported among CHC patients compared to the general population [2,8]. This is considered to be related to a personal history of high-risk behavior, such as intravenous drug abuse, alcohol abuse, high-risk sexual behavior; in intravenous drug users, an increased incidence of psychiatric disorders (98%) and suicide risk has been reported [7,9]. US veterans were repeatedly studied regarding psychiatric comorbidities in relation to HCV infection. The study concerning the most extensive veteran population [10] pointed out that 85% of the 33,842 veterans recruited had a personal history of psychiatric disorder or drug abuse.

Stigmatization and the psychosocial impact of a personal history of CHC infection increase the rate of depression among these patients. A study by Alavi *et al* [11], designed to evaluate depression prior and during treatment in 163 CHC patients, showed a rate of major depression of 36% (57 patients) and a moderate to severe suicide risk of 18% (28 patients) before treatment; depression and suicide risk were assessed by depression anxiety stress scale (DASS) score. Potential risk factors associated with depression at enrollment included unstable employment, recent injecting drug use, and poor/limited social activity.

There is also evidence that HCV infection may directly or indirectly induce biological changes in the central nervous



**Figure 1** Flow diagram of article selection for the incidence of major depressive disorders

**Table 1** Prevalence of interferon (IFN)-induced depression and suicide risk

Study	No of patients	Antiviral therapy	Duration of therapy	Scales of depression	Incidence of treatment-related depression	Suicide ideation/suicide attempt	Risk factors for depression	Outcome	Notes
Baranyi A, 2013	47	IFN-α	NR	HAMD-17 BDI	22 (53.7%)	NR	TRP depletion	NR	Biological dosing of TRP, CAA, KYN
Martin-Santos R, 2008	176	Peg-IFN and RBV	24/48 weeks	SCID-I PHQ HADS	53 (36%) 6 (8%) - MDD	NR	Alcohol abuse, immigration status, HCV genotype	1 patient discontinued treatment because of severe MDD	Depressive syndromes appeared during first 4 weeks
Pavlovic Z, 2011	74	Peg-IFN	11,4 months	HAMD-17 20-item Zung SDS	20% severe depression 36.5% minor depression	NR	Psychoactive substance abuse	NR	Peak of depressive symptoms at 12 weeks
Horikawa N, 2003	99	IFN-α	24 weeks	HAMD DSM-IV	23 (23.2%) - MDD	NR	Alcohol abuse	1 patient discontinued treatment - MDD	73.9% - onset of depression during first 8 weeks
Scalori A, 2005	185	IFN-α	4 months	MMPI	31 (17%) 8 - severe disorder	NR	Baseline MMPI pathological score	Counseling -SSRIs, IFN reduced	MMPI baseline score predicts depression
Diepernik E, 2003	42	IFN-α RBV	24 weeks	Multiple scales	23% - major depression	NR	Family history of depression	SSRIs treatment	High baseline BDI score predicted major depression
Shakoor A, 2010	100	IFN-α RBV	NR	DSM IV	39 (39%) major depression	12 (30.7%) suicide ideation (out of 39 with MDD)	NR	NR	MDD group reported also somatic symptoms
Evon DM, 2009	347	Peg-IFN-α RBV	48 weeks	CES-D	47 (12%) moderate to severe depression	14 (3.5) suicidal ideation	Younger age less social support, less education unemployment	New onset depression occurred during first few weeks of treatment	SVR was not influenced by depression
Alian S, 2013	205 with B and C virus HBV: 154 HCV: 51	IFN IFN+RBV Lamivudine	NR	BDI	41 (86%) of HCV patients	NR	NR	NR	43 (21%) of all patients had severe depression
Diepernik E, 2004	42	IFN-α RBV	24 weeks	SIGH-D BDI IDD	Suicide ideation reported	18 (43%)	History of suicide attempt	Most patients completed 6 months of antiviral treatment	Sertraline 50 mg/day
Hosoda S, 2000	943	IFN	24 weeks	DSM IV	40 (4.2%) - psychiatric symptoms	1 case	Female gender history of psychiatric disease	79% of patients with psychiatric symptoms completed antiviral therapy	12 patients required psychiatric treatment for more than 24 w after ceasing IFN
Robaeyts G, 2007	49	Peg-IFN-α RBV	48/24 weeks	20-item Zung SDS	19 (39%)-MDD	NR	History of drug abuse	NR	Depression rate higher among patients with increased score on Zung scale at 4 weeks

Contid...

Table 1 (Continued)

Study	No of patients	Antiviral therapy	Duration of therapy	Scales of depression	Incidence of treatment-related depression	Suicide ideation/suicide attempt	Risk factors for depression	Outcome	Notes
Quarantini LC, 2007	30	Peg-IFN/RBV	24 weeks	MINI	5 (16%)	No suicide attempts	History of drugs and alcohol abuse	Antiviral treatment was stopped in 1 patient due to neutropenia in the 12 <sup>th</sup> week	The risk of psychiatric symptoms is not higher during retreatment for nonresponders
Reichenberg A, 2005	50	IFN/RBV	48 weeks	CES-D	82% - MDD	NR	History of depression	34% completed all 48 weeks of therapy	The onset of depression was during first 8 weeks of treatment
Raison CL, 2005	162	Peg-IFN/RBV	24 weeks	Zung SDS	39% - moderate to severe depression	NR	History of substance abuse and depression	6 patients discontinued because of IFN-related behavioral symptoms	Baseline mood status predicts depression
Lofitis JM, 2004	39	IFN-α/RBV	24 weeks	SCID BDI	13 (33%) - MDD	NR	NR	2 patients discontinued because of psychiatric symptoms	ETR and SVR rates were higher in patients who developed IFN induced depression
Gohier B, 2003	71	IFN-α/RBV	48 weeks	HAS MADRS	22 (33%)	3 patients had suicidal ideation	Female gender, sleep disorders, prior antidepressant prescription	10% discontinued treatment; depression persisted in 8% after EOT	Regular psychiatric assessment during and after EOT is recommended
Bonaccorso S, 2002	30	IFN and RBV	3 months	MADRS DSM IV	40.7% major depression	NR	No significant gender-related differences	NR	No patient had baseline depression
Hausser P, 2002	39	IFN and RBV (Rebetron)	24/48 weeks	SCID-I BDI	13 (33.3%) - MDD	13 - suicidal ideation	Baseline BDI score predicted MDD	11/13 were responsive to antidepressant treatment	The mean time from baseline to diagnosis of MDD was 12.1 w
Alavi, 2012	111	Peg-IFN	24 weeks	MINI/DASS-21 OTI	31 (35%)	11 (10%) - suicidal ideation	History of drugs and alcohol abuse	7 (6%) discontinued therapy because of psychiatric side effects	Psychiatric side effects did not impact SVR
Yu ML, 2006	29	Peg-IFN/RBV	10.2 weeks	NR	2 (6.9%) - MDD	2 (6.9%) suicidal ideation	NR	5 (17.2) achieved SVR, 24 - nonresponders	SVR was achieved in HCV - 2 patients receiving short duration of therapy

NR, not reported; HAMD-17, Hamilton depression-rating scale -17; TRP, Tryptophan; CAA, competing amino acids; KYN, Kynurenine; SCID-I, structural clinical interview for DSM disorders; PHQ, patient health questionnaire; HADS, hospital anxiety and depression scale; MDD, major depressive disorder; 20-item Zung SDS, Zung Self-Rating Depression Scale; MMPI, Minnesota multiphasic personality inventory; SSRIs, selective serotonin reuptake inhibitors; CES-D, center for epidemiologic studies depression; SIGH-D, structured interview guide for the Hamilton depression rating scale; IDD, the inventory to diagnose depression; MINI, mini international neuropsychiatric interview; DASS, depression anxiety stress scale

system, which may trigger psychiatric disorders. Studies using proton magnetic resonance spectroscopy showed a modified creatine/choline ratio, N-acetyl-aspartate/creatine ratio, myo-inositol/creatine ratio and also an altered metabolism of these substances, changes consistent with cerebral immune activation [2]. It has also been reported that decreased dopamine and serotonin transporters binding is associated with cognitive impairment in CHC patients [2]. Pathophysiological pathways of this mechanism have not been completely understood yet, but there is recent data suggesting the possibility of HCV spreading into the central nervous system where it replicates at a low level [7].

### Depression and suicide risk in CHC patients under peg-IFN- $\alpha$ monotherapy or in combination with RBV

Suicide and suicide attempts during IFN- $\alpha$  therapy have rarely been reported mainly as isolated case reports [12-14]. Most of the studies discussing the topic of neuropsychiatric side effects of IFN- $\alpha$  therapy describe mainly the prevalence of depression, assessed by different scales; there are, however, a few studies regarding major depression complicated by psychotic episodes and suicidal ideation.

More specifically, Reichenberg *et al* [15] assessed the rates of depressive symptoms and cognitive impairment in 50 CHC patients treated with peg-IFN plus RBV over a period of 72 weeks (48 weeks of treatment and 24 weeks of post-treatment follow up); 82% of patients developed major depressive symptoms according to the Center of Epidemiologic Studies – Depression (CES-D) scale. Patients were evaluated by CES-D at baseline, at weeks 1, 2, and 4, every 4 weeks until cessation of the treatment, and at weeks 4, 8, 12, and 24 after termination of treatment.

Dieperink *et al* studied the occurrence of suicidal ideation in 55 consecutive CHC veterans treated with IFN- $\alpha$  and RBV [4]. Thirteen of the 55 veterans were part of the control group, and 42 patients received antiviral treatment. Patients undergoing IFN- $\alpha$  and RBV treatment filled in depression evaluating scales (SIGH-D, Structured Interview Guide of the Hamilton Depression Scale; BDI, Beck Depression Inventory) at baseline and at weeks 4, 8, 12, and 24. Study results show a rate of suicidal ideation during treatment presenting in 26% (11) of patients; 45% (n=5) of them required antidepressants. No patient attempted suicide during the course of treatment.

A multicenter prospective cohort study conducted by Alavi *et al* [11] evaluated the impact of IFN- $\alpha$  therapy (monotherapy) on mental health in 163 CHC patients with personal history of injection drug use, of which 111 were treated. Depressive disorder and suicide risk were evaluated prior and during (new onset) treatment by questionnaires [mini international neuropsychiatric interview (MINI); and depression anxiety stress scale (DASS)]. Of the 111 who received antiviral treatment, 88 did not have depression at study enrollment. Of these 88 participants, 31 (35%) developed new-onset depression during treatment, and 11 of 31 (35%) of these received antidepressants. Suicide risk was classified in 3 categories

according to MINI, i.e. low, moderate, and high; the highest rate of suicidal behavior was reported in week 12 of treatment (34%). Overall, 6% of participants discontinued therapy early due to psychiatric side effects. In addition, it was shown that mental health parameters (depression and/or suicide ideation) at enrollment or during treatment do not impact SVR.

A large prospective analysis conducted by Evon *et al* [16] (Virahep-C study) analyzed the effects of pre-existing depressive symptoms and occurrence of new onset depression during antiviral therapy in a sample of 394 patients. At baseline, 12% of patients had a depressive disorder, 13% were using antidepressants and no suicide ideation was reported. The incidence of new-onset depression was 26% during first 24 weeks of treatment; 4% of participants reported suicidal or homicidal ideation but without any attempts. Baseline patient characteristics which predicted new onset depression included: younger age, less social support, lower education, unemployment, and antidepressant use. The study also demonstrated no statistically significant association between incident depression and SVR rates.

Another study conducted by Barany *et al* suggested a biopsychosocial model of adverse events of IFN- $\alpha$  therapy in CHC patients, and reported new-onset depressive symptoms at a rate of 53.7% (22 of 41 patients) [17]. The study offers an insight to the pathophysiology of IFN-induced depression showing a significant enhancement of indoleamine 2,3-dioxygenase activity and an increase of kynurenine (KYN) neurotoxic metabolites during antiviral treatment. Another major finding of the study is that, as shown by the tryptophan (TRP)/competing amino acids quotient, TRP availability to the brain declines in patients with IFN- $\alpha$  treatment-related depressive symptomatology, suggesting a need of higher TRP to stabilize their mood.

A recent study conducted by Alian *et al* [18] analyzing the correlation of depression with hepatitis drugs in 205 patients with chronic hepatitis B and C, reported a prevalence of depression among IFN-treated patients of 100% vs. 94.4% in patients receiving IFN plus RBV treatment. Depression was also more frequent in CHC than chronic hepatitis B patients (86.3% vs. 68.8%, respectively).

A temporal analysis of symptoms occurring during IFN- $\alpha$  therapy revealed different times of onset for the neuro-vegetative/somatic vs. mood/cognitive symptoms. Different symptoms (fatigue, decreased appetite, and pain) develop at early stages of treatment, during the first weeks of therapy and persist throughout the whole duration of therapy [19]. Cognitive impairment and mood disorders (depressive symptoms, anhedonia, memory disturbances) develop at later stages of treatment (after week 4), with an increasing intensity of depressive symptoms after 8 weeks of therapy.

The study led by Diepernik *et al* which examined the occurrence of suicide ideation among patients untreated and treated with IFN- $\alpha$ 2b, showed a peak of suicide ideation during weeks 8 and 12 [4]. As already mentioned, Alavi *et al*, who examined the impact of IFN- $\alpha$ 2a treatment on the mental health during recent HCV infection, considered that the maximum suicidal risk occurs during week 12 of treatment [11]. The prospective 72-week study by Reichenberg

*et al.*, discussed previously, outlined an increase in depressive symptomatology over the first 8 weeks of treatment, with a minor decrease after week 8, and increasing again in the last 12 weeks of treatment; 39% of patients developed new-onset major depressive disorder by week 8, 52% during the 28th week of treatment and 55% during week 40.

Most neuropsychiatric side effects resolve after the end of treatment; however, cases of persistent or newly developed major depressive disorders associated with suicide attempts occurring after cessation of therapy have been reported. Riflet *et al.* published 5 cases of suicide attempts in CHC patients treated with IFN- $\alpha$ ; in case of two of these patients depressive symptoms did not resolve after the end of therapy, and another two patients developed depressive disorder after cessation of IFN- $\alpha$  treatment [12].

### Pathophysiology of IFN-induced depression

The pathophysiology of neuropsychiatric side effects occurring during IFN- $\alpha$  therapy, although not completely elucidated yet, involves two main mechanisms: impairment of monoamines metabolism and neuroendocrine dysfunction [2]. Recent studies showed that immune mediators, including IFN- $\alpha$ , induce significant changes in enzymatic pathways involved in monoamines metabolism (serotonin, dopamine, norepinephrine). These alterations imply the activation of indoleamine-2,3-dioxygenase which rushes TRP catabolism, decreases 5-hydroxytryptamine (5-HT) serum levels, following an increase in 5-HT neurotoxic metabolites: KYN and quinolinic acid [2,8,20]. These changes have been shown to correlate with the onset of depressive symptomatology; moreover, there is evidence of a normalization of TRP and KYN serum levels 6-12 months after cessation of IFN- $\alpha$  therapy which correlates with the resolution of depressive symptoms [21]. An alteration of cerebrospinal fluid levels of 5-hydroxyindoleacetic acid during IFN- $\alpha$  therapy has also been observed, associated with increased rates depressive disorders [9].

Another mechanism which may explain neuropsychiatric adverse events of IFN- $\alpha$  therapy involves changes in the serum levels of adrenocorticotrophic hormone (ACTH) and cortisol. A prospective study conducted by Raison *et al.* examined the diurnal activity of the hypothalamic-pituitary axis and proinflammatory cytokines in 33 CHC patients prior and 12 weeks following IFN- $\alpha$  and RBV therapy. Depressive symptomatology was also evaluated by Montgomery-Asberg Depression Rating Scale. Results of the study showed a flattening of ACTH levels and a decrease in cortisol concentration during the day, and a nocturnal peak of cortisol and ACTH levels, which correlated with an increase in depressive symptomatology and fatigue [22].

### Psychiatric management of CHC patients treated with IFN- $\alpha$

Psychiatric disorders occurring during IFN- $\alpha$  therapy, mostly major depressive disorders, may lead to suicide ideation

and/or suicide attempts; this is why a thorough psychiatric evaluation, including depression assessment scales or criteria, namely International Classification of Diseases (ICD-10) and The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), are required before the initiation of IFN therapy to identify high-risk patients. Predictive factors for IFN- $\alpha$ -induced depression include: personal history of depressive disorder, family history of psychiatric disorders, early onset of symptoms (sleep disturbance, loss of appetite), baseline stress, lack of social support, depression during previous IFN treatment, and increased serum levels of proinflammatory cytokines (interleukins -10 and -6, and tumor necrosis factor-receptor-1) [2,17].

The ELPA (European Liver Patient's Organization) organized a European expert conference (2011 EASL meeting) to review the medical literature concerning the management of psychiatric disorders in CHC patients and to develop expert recommendations. It is recommended to perform a detailed psychiatric evaluation of CHC patients prior to introducing IFN- $\alpha$  therapy, which includes personal history of psychiatric comorbidity, addictive behavior, previous suicide attempts, and psychosocial functioning; it is also required to inform the patient about the neuropsychiatric adverse events likely to occur during IFN- $\alpha$  therapy. Close monitoring should be performed every 4, 12 weeks, or even more frequently (every 2-4 weeks) when required (new-onset mood disorders, drug/alcohol abuse, personal history of psychiatric comorbidity). Considering that suicide risk is the highest during first 12 weeks of therapy, closer follow up is recommended during this interval.

The pharmacological management of adverse events depends on the time when they occur. Sleep disturbance, as a risk factor for depressive symptoms occurrence, requires early therapeutic management. Data shows that 10-14% of patients discontinue IFN- $\alpha$  therapy because of fatigue, mood disorders, and sleep disturbance [9]. Regarding the efficacy of the antidepressants, studies have shown that selective serotonin re-uptake inhibitor (SSRI) therapy decreased the severity of depressive symptoms by 50%, with an antidepressant treatment response rate of more than 85% after 5-6 weeks of therapy [23]. It is also recommended that antidepressant therapy to continue 6 to 12 weeks after IFN- $\alpha$  cessation therapy because of the risk of depressive disorders, suicide ideation or cognitive disorders recurrence [2,9,12]. However, initiation of antidepressant therapy should consider drug-drug interactions, underlying hepatic function, the possibility of drug induced hepatotoxicity and other adverse side effects [24].

### Prevention of IFN- $\alpha$ -induced depression

Given the evidence of decreased serotonergic neurotransmission as a pathophysiological mechanism of IFN- $\alpha$ -induced depression, the administration of SSRIs was considered as a strategy for treatment and prevention of IFN- $\alpha$ -induced depression. In a study led by Schaefer *et al.* [25] on 14 psychiatric CHC patients receiving prophylactic treatment

with citalopram (20 mg/day) before and during IFN- $\alpha$  therapy, a lower incidence of major depressive disorder was reported compared to the two control groups (CHC patients with and without psychiatric disorders who did not receive prophylactic antidepressant therapy). Major depression during the first 24 weeks of IFN- $\alpha$  therapy was 14% in the group who received citalopram vs. 64% and 55% in the control groups. Another study focused on 10 patients with previous history of IFN- $\alpha$ -induced depression, who received antiviral re-treatment with peg-IFN and RBV and prophylactic SSRIs 3 weeks before the initiation of antiviral treatment, reported a lower incidence of IFN-induced depression compared to the first therapeutic regimen [26]. There are also several prospective trials which show contradictory data [27-30], merely due to methodological issues: small groups of patients, lack of consistent follow up (one study evaluated depression only for the first 3 months of antiviral treatment). However, in spite of the heterogeneous data, antidepressive prophylaxis (escitalopram, citalopram and paroxetine) was reported to be well tolerated and does not affect SVR.

Antidepressant prophylaxis must be continued during the course of antiviral therapy and up to 12 weeks after discontinuation. According to the expert consensus statement (EASL 2012), not every CHC patient undergoing antiviral therapy should be administered antidepressant pretreatment; every case must be evaluated in a customized fashion [2]. This approach would improve the quality of life of CHC patients, impaired before but also under IFN therapy [31-33].

The advent of non-IFN regimens is expected to decrease the number of psychiatric side effects including suicide.

### Limitations of the study

In present there is considerable variability of frequency and extent of IFN-induced depression reported in different cohorts of patients. A recent study conducted by Schafer *et al* [34] systematically reviewed recent literature to identify to what extent methodological bias contributed to inconsistent results in different studies. The results showed that variability of findings is mainly due to different study populations, treatment regimens (IFN monotherapy vs. IFN plus RBV), methodological approaches and different screening instruments for depression, particularly cut-off criteria for clinically relevant depression. Thus, inconsistency of results between studies may be justified. Further research in this field necessitates the use of standardized assessment and objective criteria and guidelines in clinical practice for treatment of IFN-induced depression. Although IFN is no more recommended for CHC therapy [35] in many countries it is still the available alternative and there are patients still continuing IFN therapy. Knowing the depressive and suicidal side effects of IFN is still important.

### Concluding remarks

Psychiatric side effects associated with IFN- $\alpha$  therapy in CHC patients are the main cause of antiviral treatment

discontinuation, which results into a decreased rate of SVR. By far, the most common side effect of IFN- $\alpha$  therapy is depression; major depression disorder and new-onset psychosis may lead to suicide ideation and suicide attempt. Given this fact, a careful psychiatric evaluation is required prior to initiation of IFN therapy to identify high-risk patients. Therefore, in selected cases antidepressant therapy as a prophylactic measure should be considered.

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