BRIEF REPORT

Is the interferon-α-triggered depressive episode a self-limited kind of depression? Four cases of persistent affective symptoms after antiviral treatment in HCV-infected individuals

AMANDA GALVÃO-DE ALMEIDA1,2, LUCAS C. QUARANTINI1, SUSANA BATISTA-NEVES1, ANDRÉ C. LYRA4, RAYMUNDO PARANÁ4, IRISMAR R. DE OLIVEIRA1, ÂNGELA MIRANDA-SCIPPA1 & CAMILA GUINDALINI2,3

1Department of Neurosciences and Mental Health, Universidade Federal da Bahia, Teaching Hospital – Psychiatry Service, Bahia, Brazil, 2Department of Psychiatry and Laboratório Interdisciplinar de Neurociências Clínicas (LiNC), Universidade Federal de São Paulo, São Paulo, Brazil, 3Department of Psychobiology, Universidade Federal de São Paulo, São Paulo, Brazil, and 4Department of Gastroenterology, Universidade Federal da Bahia, Bahia, Brazil

Abstract

Objectives. To discuss relevant aspects in a series of cases in which interferon-α-triggered depressive symptoms persisted up to 4 years after therapy cessation in HCV-infected patients. Methods. Two experienced psychiatrists (AGA and LCQ) identified these four cases in a systematic evaluation program of HCV patients in the Hepatology Unit of the Teaching Hospital at the Federal University of Bahia, Brazil. Lifetime psychiatric diagnoses were confirmed by the Mini International Neuropsychiatric Interview (MINI Plus), and a questionnaire was submitted in order to gather clinical and sociodemographic characteristics. Results. In three out of the four cases identified, major depression diagnosis was reached after more than 12 months of interferon-α therapy interruption and, in one case, depression recurred 6 months after antiviral treatment cessation in a patient on antidepressants. The only case that referred a past history of psychiatric diagnosis reported no offer of mental health care despite the presence of a major depressive episode with psychotic features and suicidal behaviour during the cytokine usage. Conclusions. Interferon-α-triggered depression may remain undiagnosed even in tertiary university hospitals, may persist years after the antiviral therapy cessation, and may recur even in patients on adequate antidepressant treatment.

Key words: Interferon-α, hepatitis C, major depressive disorder, cytokines, adverse effects

Introduction

Interferon-α (IFN-α), conventional or pegylated (Peg-IFN-α), in combination with ribavirin (RBV), constitutes the only Food and Drug Administration (FDA)-approved treatment for chronic infection with hepatitis C virus (HCV). In clinical trials, 46–80% of HCV patients treated with combination therapy achieve a sustained viral response (SVR), defined as undetectable HCV in the blood 6 months following the end of treatment (Asnis and De La Garza 2006).

Despite its potential therapeutic benefits, administration of IFN-α frequently prompts the appearance of neuropsychiatric symptoms, e.g., depressed mood, anhedonia, anxiety, psychosis, suicidal behaviour, acute dystonia and cognitive impairment, as well as neurovegetative and somatic symptoms, e.g., anorexia, fatigue, psychomotor slowing, altered sleep, headache, increased sensitivity to pain, and fever (Asnis et al. 2003; Capuron and Miller 2004; Quarantini et al. 2006, 2007; Wobrock et al. 2009).

Reports on depression rates during IFN-α treatment vary broadly. However, clinical studies that used standard Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria have shown that approximately 30–45% of patients receiving IFN-α develop a major depressive episode (MDE) (Capuron...
et al. 2002; Asnis and De La Garza 2006). This psychiatric adverse effect may result in severe outcomes, such as the presence of suicidal behaviour during the course of the therapy, compliance compromise, and the likelihood of leading to dose reduction or interruption of the therapy (Capuron et al. 2002). Furthermore, depression seems to represent an independent risk factor for poor virological response (Raison et al. 2007).

According to the criteria of the latest version of DSM, an MDE arising during a pharmacological treatment known by its depressogenic properties (e.g., interferon, propranolol), is designated as a substance-induced mood disorder with depressive features (Asnis and De La Garza 2006). In addition, although depressive symptoms that emerge during IFN-α treatment generally resolve after treatment cessation, there are some accounts of residual affective symptoms (Capuron et al. 2002), and even worsening of depression (Rifflet et al. 1998; Loftis and Hauser 2004), following withdrawal from antiviral therapy. Nevertheless, when psychopharmacotherapy is required, IFN-α-induced MDE is remarkably responsive to antidepressants, and symptomatic response appears to occur more rapidly than usually seen in traditional major depressive disorder (Keefe 2007).

Although many studies emphasize the incidence rates and the consequences of IFN-α-induced depression, little attention is given to the possible chronicity and to the late outcomes of this neuropsychiatric adverse effect. In the present article, we focus on these points and report four cases in which depressive symptoms persisted up to 4 years after IFN-α therapy cessation in HCV-infected patients (Table I).

**Methods**

Two experienced psychiatrists (AGA and LCQ) identified these four cases in a systematic evaluation program of HCV patients in the Hepatology Unit of the Teaching Hospital at the Federal University of Bahia, Brazil. This program includes a continuous psychological support to HCV individuals under antiviral treatment, sending those with clinical evidence of depressive symptoms for a standardized psychiatric evaluation. This systematic evaluation also contains a cross-sectional study in which all HCV patients who have completed IFN-α/RBV therapy are invited to participate in a neuropsychological and psychiatric assessment.

Lifetime psychiatric diagnoses were confirmed by the Mini International Neuropsychiatric Interview, Brazilian version 5.0.0 (MINI Plus) (Amorim 2000), which encompasses the main Axis I disorders of DSM-IV (American Psychiatric Association 1994) and International Classification of Diseases (ICD-10; World Health Organisation – WHO 1992). Beck Depression Inventory (BDI) was used to assess the severity of the depressive symptoms. A questionnaire was submitted in order to gather clinical and socio-demographic characteristics. Medical charts were also consulted to guarantee that we had obtained the best information available.

The study was approved by the local Medical Review Ethics Committee and performed in accordance with the ethical standards set in the 1964 Declaration of Helsinki. Additionally, all patients had provided written informed consent prior to their inclusion in the study.

**Results**

**Case 1**

A 50-year-old, divorced afro-descendent man, with a high school degree, living alone and referring a family history of depression and addiction to alcohol. At the time of evaluation, he was unemployed and receiving no financial support from the government.

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Age</th>
<th>HCV genotype</th>
<th>Probable way of acquisition</th>
<th>Persistence of depressive symptoms after cessation of IFN-α treatment (m)</th>
<th>Result of IFN-α treatment</th>
<th>Current psychiatric diagnosis</th>
<th>Past psychiatric diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>50</td>
<td>1</td>
<td>Accidental wound</td>
<td>24</td>
<td>No response</td>
<td>IFN-α induced MDE</td>
<td>Alcohol dependence</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>51</td>
<td>1</td>
<td>Sharing shaving blades</td>
<td>14</td>
<td>No response</td>
<td>IFN-α induced MDE</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>58</td>
<td>1</td>
<td>Unknown</td>
<td>48</td>
<td>No response</td>
<td>IFN-α induced MDE</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>46</td>
<td>1</td>
<td>Blood transfusion</td>
<td>6</td>
<td>Response</td>
<td>IFN-α induced MDE</td>
<td>None</td>
</tr>
</tbody>
</table>

M, male; F, female; m, months; MDE, major depressive episode.
This patient had been diagnosed with HCV 7 years before the evaluation, was Child-Pugh A, and the hepatic biopsy revealed stage 2 fibrosis, according to the METAVIR classification (Bedossa and Poynard 1996). Although this patient has referred that the first depressive symptoms had developed during the third week of IFN-α treatment, no health professional detected them during or right after the antiviral therapy. This fact is remarkable considering that he had presented a severe depression with psychotic features, such as visual and auditory hallucinations, and tried to shoot himself during the course of the therapy.

At this evaluation, 2 years after cessation of IFN-α therapy, the interview with the MINI Plus indicated the diagnosis of MDE with a current low suicide risk, although the patient still scored for severe depression, 48 on the BDI.

**Case 2**

A 51-year-old afro-descendent man, married, who had not completed the primary school, living with his family, and not reporting a family history of psychiatric disorder. He was also unemployed without governmental support. Three years prior to this evaluation, he had had a diagnosis of HCV infection, showing that he was Child-Pugh A and had hepatic fibrosis stage 3. This patient referred the onset of the MDE during the first month of IFN-α treatment and had never been submitted to a psychiatric interview. At this evaluation, we detected an MDE with a high suicide risk according to the MINI Plus, and he scored 45 on the BDI (severe depression).

**Case 3**

A 58-year-old female teacher, divorced, living with her sister. She was also Child-Pugh A, referred the first depressive symptoms during the beginning of standard IFN-α/RBV therapy 10 years ago, and presented a progressive worsening of the depression during the course of the antiviral treatment. She did not complain about the affective symptoms to the hepatologist and abandoned the clinical follow-up, discovering, 4 years after the therapy cessation, that the antiviral treatment had been unsuccessful. During this period, the patient referred recurrent depression (two other episodes) and residual symptoms among relapses, but confirmed she had not sought psychiatric or psychological care.

Because of the increased fibrosis diagnosed by liver histology in 2005, a hepatologist decided to start a new treatment with Peg-IFN-α plus RBV. Before starting antiviral therapy, she was evaluated in the Psychiatric Unit and a treatment with paroxetine (40 mg/day) was started. She remitted 6 weeks later and was able to start the second antiviral therapy. During the treatment, she remained on paroxetine and only a transitory sleep disturbance occurred, disappearing with lorazepam (1 mg/night). She completed the antiviral therapy with no depressive recurrence, but viral clearance was not achieved. Two attempts to discontinue the antidepressant by the patient, after Peg-IFN-α trial, were followed by recurrence of depressive symptoms, leading to the maintenance of paroxetine at a dose of 40 mg/day.

**Case 4**

A 46-year-old female secretary, married, Child-Pugh A, developed a depressive mood, associated with suicidal thoughts, 2 months after beginning the antiviral therapy. Psychiatric evaluation classified the episode as first MDE, and treatment efforts with mirtazapine (up to 45 mg/day) led to remission of symptoms in 4 weeks. Three weeks before the end of IFN-α therapy, depressive symptoms, including suicidal thoughts, relapsed. Venlafaxine was introduced (up to 150 mg/day), with the maintenance of mirtazapine at the same dose, and antiviral treatment was interrupted. Three weeks later, this patient responded to the antidepressants and, after a further 2 weeks, she was in remission of depressive symptoms. Six months after the interruption of IFN-α, she started to complain about a lack of motivation, inactivity, repeated episodes of depressed mood, significantly disturbing her quality of life and performance during work time. The dose of venlafaxine was increased to 225 mg/day. During the next 6 weeks, she showed significant improvement, and remained under psychiatric treatment.

**Discussion**

To our knowledge, this is the first report of IFN-α-triggered depression cases detected more than 12 months after the therapy interruption (cases 1, 2 and 3) or focusing on the recurrent pattern of this MDE after antiviral cessation in a patient undergoing antidepressant treatment (case 4).

There are few reports of severe depressive episodes, including psychotic features and suicidal behaviour, during (Ademmer et al. 2001; Sockalingam and Balderson 2005) and after IFN-α therapy cessation (Riflet et al. 1998). A recent prospective study aimed to evaluate the long-term changes of mental health after IFN-α treatment in HCV patients. The authors ratified that pre-existing psychiatric disorders or depressive mood are risk factors for psychopathological changes during antiviral therapy, but
conversely, they found that significant long-term impairment in mental health occurred in the patients with the lowest pre-treatment depression scores and without psychiatric problems (Schmidt et al. 2009). Our report is in line with those findings since, according to the diagnostic interview that was performed and to the patients’ medical charts, three out of four individuals presented no past psychiatric antecedents, and none referred any dysfunctional affective symptom immediately before antiviral therapy.

Our study highlights the undiagnosed depression in three cases, during and after antiviral treatment, despite the fact that these patients were receiving regular medical assistance. According to the literature, recognition of psychiatric disorders in patients with chronic and/or severe general medical conditions, especially major depression, can be challenging for clinicians, and the occurrence of this comorbidity affects the quality of life and the course of the somatic illness (Batista-Neves et al. 2009; de Jonge et al. 2009). Moreover, the efficient detection of psychiatric symptoms in HCV patients is particularly important since individuals with baseline depressive complaints seem to be the ones at higher risk to develop affective disorders during IFN-α therapy (Keefe 2007). In fact, our group has already reported that 26 out of 90 HCV individuals presented a current mental disorder, even at least 3 months without IFN-α treatment, 84.6% of which had gone undiagnosed (Batista-Neves et al. 2008).

Through this report, we also intend to question the transient character of the IFN-α-induced depression. Usually known to be limited to the regular 6–12 months of treatment (Capuron et al. 2002), this adverse effect may impose persistent psychopathology and damage to some depressed patients. According to the idea supported by most studies, if pathophysiological mechanisms that generate and maintain the depressive symptoms during treatment would depend on the direct and indirect actions of IFN-α on the central nervous system (Capuron and Miller 2004), then these adverse side effects should progressively disappear after the treatment interruption. Despite this, some reports and studies emphasize that IFN-α-induced depression may persist after the end of the cytokine exposure (Rifflet et al. 1998; Capuron et al. 2002; Gohier et al. 2003; Loftis and Hauser 2004). Therefore, we hypothesized that, in some vulnerable patients, IFN-α may trigger a pathophysiological pathway which may become autonomous and maintain the depressive symptoms, even in the absence of the exogenous cytokine.

After all these considerations, we can also speculate that this cytokine may function as an “immunological trauma” that triggers a vulnerable neural circuit and generates a chronic depressive episode or, through the kindling effect, causes an individual without a history of past depression to become a patient with a recurrent depressive disorder.

Additionally, even though hepatitis C brings upon itself a burden (e.g., prejudice, transmissible infection, way of acquisition associated with i.v.-drug use), and its consequences (e.g., unemployment, divorce, social isolation) may play a role in the development and maintenance of depression in HCV-infected individuals, the role of biological mechanisms has been emphasized in the pathophysiology of this depressive disorder (Sockalingam and Abbey 2009). More specifically, since these adverse conditions are common for the majority of patients with HCV, it is currently speculated that individual genetic variations may explain why the minority of HCV patients develop depression during IFN-α therapy (Pierucci-Lagha et al. 2010), and an even more reduced number persists with relevant and dysfunctional depressive symptoms after the treatment termination.

Further discussion on this complex matter is beyond the scope of this report; nevertheless, our purpose is to raise these questions and to emphasize the need of investigation of persistent IFN-α-triggered depression.

The main limitation of our report is that these patients were not evaluated before the antiviral therapy; consequently, we cannot affirm that depressive symptoms began only after cytokine initiation. In order to prevent memory bias in the detection of IFN-α-triggered depression, we intend to include systematic, pre-treatment assessments in our evaluation program.

Finally, in a recent review, we have found that systematically pre-treating HCV patients with antidepressants before initiating antiviral therapy is not effective to prevent depression (Galvão-de Almeida et al. 2010). Therefore, it is fundamental to prepare clinicians to better differentiate a neurovegetative syndrome from a complete depressive syndrome, during and after the cytokine therapy, in order to increase the detection of this affective disorder. Consequently, this practice could avoid the unfavorable outcomes of a chronic and untreated mood disorder.

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Statement of interest

The authors have no conflict of interest with any commercial or other association in connection with the submitted article.

References


