Liver International ISSN 1478-3223

CLINICAL STUDIES

Incidence of psychiatric side effects during pegylated interferon-α retreatment in nonresponder hepatitis C virus-infected patients

Lucas C. Quarantini[1,2], Rodrigo A. Bressan[2], Amanda Galvão[1], Susana Batista-Neves[1], Raymundo Paraná[1] and Ângela Miranda-Scippa[1]

1 University Hospital, Federal University of Bahia School of Medicine, Salvador-Bahia, Brazil
2 Laboratório Interdisciplinar de Neurociências Clínicas (LiNC), Federal University of São Paulo, São Paulo, Brazil

Keywords
comorbidity – hepatitis C – interferon – psychiatric side effects – retreatment

Correspondence
Lucas C. Quarantini, Rua Altino Seberto de Barros 241/404 Itaigara, Salvador-Bahia, 41825-010, Brazil
Tel/Fax: 55 71 33514111
e-mail: lcq@ufba.br

Received 12 December 2006
accepted 8 April 2007

DOI:10.1111/j.1478-3231.2007.01532.x

Abstract

Objective: Evaluate the incidence of mental disorders using pegylated interferon plus ribavirin retreatment in nonresponder hepatitis C virus-infected patients. *Method:* The Mini-International Neuropsychiatric Interview (MINI) was used to evaluate 30 hepatitis C virus-infected interferon-nonresponder patients at baseline and following 4, 12 and 24 weeks of pegylated interferon retreatment. *Results:* During the pegylated interferon/ribavirin retreatment, 5(16.6%) patients developed psychiatric side effects: 3(10%) were diagnosed with major depressive disorder, 1(3.3%) had a brief psychotic disorder and 1(3.3%) presented with panic attacks. *Conclusion:* This is the first prospective study evaluating the incidence of neuropsychiatric side effects during interferon retreatment of hepatitis C virus-infected patients, suggesting that the risk of acquiring serious psychiatric symptoms during retreatment with interferon-α (IFN-α) may not be higher than during the first antiviral therapy. This finding challenges the hypothesis that during a second treatment with IFN-α, patients with hepatitis C may be at greater risk for neuropsychiatric side effects than naïve patients.

Interferon-α (IFN-α) has been used in combination with ribavirin (RBV) in the treatment of patients with hepatitis C virus (HCV), resulting in sustained virological response (SVR), in about 50% of patients (1–5). However, among patients with HCV genotype 1 infection treated for 48 weeks, the rate of SVR is lower than 30% (6). A new preparation of pegylated IFN-α (PEG IFN), both α-2a and α-2b have an extended half-life and appear to increase rates of sustained viral response, while offering the convenience of once-a-week dosing (1). The adverse events reported with the use of the two drugs were similar, because these are structurally similar products (7).

Retreatment with IFN-α is often necessary to obtain the necessary viral eradication. Despite its therapeutic benefit, many studies report that repeated administration of IFN-α in patients with chronic active hepatitis may induce neuropsychiatric side effects, especially symptoms of major depression (8). In selected cases, treatment might be reduced or interrupted, directly affecting the outcome, because adherence to IFN-α therapy is essential to achieving a SVR. Thus, a decrease in side effects during therapy with IFN-α should lead to a higher compliance rate among patients and have the best antiviral efficacy (9).

Several risk factors are thought to increase the probability of emergent psychiatric comorbidity during IFN-α treatment, such as previous history of psychiatric illness, history of substance abuse, family history of psychiatric illness and history of suicidal ideation. Although these factors are not well validated, they have been used as exclusion criteria in several large HCV clinical trials (10). Several studies demonstrated that gender is not a risk factor for developing depressive symptoms during IFN therapy (11–14); however, not all studies corroborate this finding (15). Only one study indicated advanced age as a risk factor for major depression (14). RBV has also been reported to be associated with increased depression. Therefore, RBV and IFN might be independently associated with the occurrence of depressive symptoms in the treatment of HCV-infected patients (13, 16, 17).

There is reason to believe that IFN-α retreatment represents an additional risk factor to the occurrence of depression. There is evidence that administration of

this cytokine activates corticotrophin-releasing factor (CRF) production (18) and increases the cerebrospinal fluid concentration of CRF, which are common findings among depressive patients (19). In addition, there is experimental evidence suggesting that a second exposure to a stressful stimulus can sensitize the hypothalamic–pituitary–adrenal (HPA) axis and produce an exacerbated glucocorticoid response (20). Therefore, it is reasonable to hypothesize that a second IFN-α exposure could increase the rate of depression among HCV-infected patients. IFN-α antiviral retreatment has already been suggested as a potential risk factor to depression in this population (21). However, we could not find in any study the literature evaluating psychiatric side effects during IFN retreatment in HCV-infected individuals.

Therefore, we have designed the first study to prospectively evaluate the incidence of mental disorders during PEG IFN/RBV retreatment in HCV-infected patients nonresponders to the first antiviral treatment.

Methods

Subjects

Hepatitis C virus-infected patients who did not respond to previous antiviral treatment for at least 24 weeks with conventional IFN-α 3–6 million units three times weekly in combination with 900–1200 mg/day of RBV were recruited from the northeastern region of Brazil. Thirty patients volunteered to participate and completed psychiatric evaluations before and during therapy. Follow-up of the subjects was conducted at a local academic medical centre (Gastro-Hepatology Unit, Federal University of Bahia School of Medicine). Twenty-four patients received PEG IFN-α-2b (1.5 μg/kg/week) plus RBV (1.200 mg/day) and six received PEG IFN-α-2a (180 μg/week) plus RBV (1.200 mg/day). The diagnoses were based on marker positivity (HCV RNA-PCR) and liver biopsy. All patients had compensated liver disease but elevated serum alanine aminotransferase levels. Exclusion criteria were pregnancy, history of depression (including depression during the previous IFN/RBV treatment), other current and past mental disorders, autoimmune disorder or any cause for liver disease other than HCV. Subjects with a history of substance abuse were required to be abstinent for at least 6 months before study entry. Patients who maintained positivity (HCV RNA-PCR) after 12 weeks of retreatment were excluded from the study.

Procedures

Patients were evaluated at baseline and following 4, 12 and 24 weeks of PEG IFN retreatment with the Mini-International Neuropsychiatric Interview (MINI); a short, structured diagnostic psychiatric interview for Diagnostic and Statistical Manual of Mental Disorders, fourth Edition (DSM-IV) disorders, validated to Portuguese, was used to exclude previous and present mental disorders (22).

Antidepressant administration was dictated by clinical judgment. This study was approved by the Medical Review Ethics Committee of the Federal University of

Table 1. Baseline characteristics of 30 study patients

Characteristics	
Age at beginning of IFN therapy (years; mean ± SD)	49.02 ± 7.69
Gender	
Male, *N* (%)	25 (83.3)
Female, *N* (%)	5 (16.7)
Weight (kg ± SD)	76.12 ± 11.6
Genotype	
1, *N* (%)	22 (73.3)
3, *N* (%)	8 (26.7)
PEG IFN-α-2a, *N* (%)	6 (20)
PEG IFN-α-2b, *N* (%)	24 (80)
Cirrhotic (%)	15 (50)
Risk factor for HCV	
Unknown (%)	13 (43.3)
IVDU (%)	3 (10)
Transfusion (%)	8 (26.7)
Contaminated instruments (%)	5 (16.7)
Tattoo (%)	1 (3.3)

HCV, hepatitis C virus; IVDU, intravenous drug use; PEG IFN, pegylated interferon-α.

Bahia, Brazil. All subjects provided written informed consent.

Data were registered and analysed using the Statistical Package for Social Sciences (SPSS for Windows, version 9.0; SPSS, Chicago, IL, USA). Because of the explorative character of the study, sample size was not calculated before the study. Data describing quantitative measures are expressed as median or mean ± SD unless indicated otherwise. Qualitative variables are presented as counts and percentages.

Results

Table 1 summarizes the baseline characteristics from the 30 patients with HCV. Three patients (10%) had a history of substance-abuse treatment for intravenous (i.v.) drug use and one for alcohol dependence. Two patients also had criteria for abuse of cannabis and two for alcohol (one of these is the same former i.v. drug user).

The number of patients who developed mental disorders during the retreatment was five (16.6%). One patient (3.3%) was diagnosed as having a brief psychotic disorder, three patients (10%) were diagnosed as having major depression and one patient (3.3%) presented with four panic attacks. No manic or delirium episodes occurred during the retreatment period (see Table 2).

The patient with psychosis first showed symptoms at the beginning of the second month of retreatment. Risperidone (2 mg/day) was prescribed and the first signs of improvement appeared by the end of the first week. The patient's delusional symptoms significantly improved by the end of the second week and total recovery was obtained in a month. Patients who presented with major depression experienced the first symptoms between the 12th and 18th weeks. One patient refused to take antidepressants and followed a weekly programme of cognitive behavioural therapy during treatment. The other two used mirtazapine (30 mg/day), presenting remission of the depressive symptoms within approximately 4 weeks, and stopped using the antidepressant 2 weeks after the end of retreatment. The patient who presented with panic attacks was successfully treated with alprazolam (2 mg/day), which was discontinued at the end of the antiviral retreatment. As was used in the above-described depressive patient, cognitive therapy has also been tested as a treatment option in patients who exacerbate panic attacks during IFN treatment (23).

The dose of IFN was not reduced in any of the cases above.

Antiviral treatment was stopped in one patient due to neutropenia in the 12th week. Seven other patients discontinued retreatment because they did not present early virological response in the 12th week.

Discussion

To our knowledge, this is the first study evaluating the incidence of mental disorders in HCV-infected non-responder patients undergoing PEG IFN retreatment. We found a low incidence of psychiatric side effects: five patients (16.6%), including three (10%) cases of DSM-IV-defined major depressive disorder. Several authors have previously reported a high incidence of depression, between 20% and 44%, during IFN therapy (11, 14, 17, 21, 24). Nevertheless, the present retreatment study is consistent with the rates of 5%, 10% and 12% obtained in three first-treatment studies of patients with chronic viral hepatitis who were assessed prospectively using validated psychiatric scales (25–27). There may be several reasons to explain the low rates of drug-induced psychiatric disorders in our sample. The low frequency of history of i.v. drug use among our sample is consistent with a prior report regarding the route of infection in Brazil, where the use of a vitamin complex injection is common (28). The use of i.v. drugs is the most common route of hepatitis transmission in the USA and the incidence of depression is remarkably high among this population with hepatitis C (29, 30). The exclusion of patients with current and previous mental diagnosis, including the first antiviral treatment period, might have selected a sample with a lower risk for depression during IFN-α treatment (8, 12, 21, 31–33). Other studies indicated that only patients with high baseline scores of depression had more intense depressive symptoms during the use of IFN-α (17, 26, 34). Taken together, our low incidence of major depressive disorder may be

Table 2. Psychiatric diagnosis during pegylated interferon-α therapy

Diagnosis	*n*	%	Week of first symptoms	Time to remission (weeks)
Major depressive disorder	3	10	12–18	4
Brief psychotic disorder	1	3,3	5	4
Panic attacks	1	3,3	4	1

explained by the fact that we have excluded patients with two important risk factors: i.v. drug users and history of depression.

The causes of depressive mood changes and neuropsychiatric symptoms, such as psychomotor slowing, anergia/fatigue, parkinsonism and dystonia during IFN-α therapy, are still not well understood and are probably multifactorial. The pathophysiological mechanisms of these symptoms may involve alterations in basal ganglia circuitry and dopamine pathways (35, 36), neurochemical serotonergic pathways, HPA changes and cytokine network activation (37).

The present study has some limitations, such as a relatively small sample size, the lack of a control group and the small number of i.v. drug users. Although this study does not allow generalization to the i.v. drug using population, it is the first prospective assessment of psychiatric morbidity in IFN-α retreatment and presents original information regarding the safety profile of this treatment.

The results of this study suggest that the risk of acquiring serious psychiatric symptoms during retreatment with IFN-α may not be higher than during the first antiviral therapy. Further research is needed to clarify the risk factors of IFN-associated neuropsychiatric symptoms.

Acknowledgements

This study was partially supported by a grant of the Foundation for the Support of Research in the State of Bahia: 195712163383 (FAPESB, Brazil). The authors thank the patients for their participation and the members of the Association of HCV-infected Individuals Vontade-de-Viver. They also thank Dr Maria Isabel Schinoni, Dr Simone Cunha, Dr Viviane Mello and Ana Thereza Britto Gomes for clinical assistance and Alberto Junqueira for technical assistance. Part of the material presented here is taken from the doctoral thesis of Lucas C. Quarantini (in preparation).

References

1. Manns MP, Mchutchison JG, Gordon SC, *et al*. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. *Lancet* 2001; **358**: 958–65.
2. Fried MW, Shiffman ML, Reddy KR, *et al*. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; **347**: 975–82.
3. Steindl-Munda P, Ferenci P, Austrian Hepatitis Study group *et al*. Impact of high-dose interferon induction and ribavirin therapy in patients with chronic hepatitis C relapsing after or not responding to interferon monotherapy. *Liver Int* 2003; **23**: 269–75.
4. Boucher EJ, Jacquelinet S, Canva V, *et al*. High rate of long-term virological response after a 1-year course of interferon+/– ribavirin in chronic hepatitis C relapsers. Results of a 191 patients randomized trial. *Liver Int* 2003; **23**: 255–61.
5. Chuang WL, Dai CY, Chen SC, *et al*. Randomized trial of three different regimens for 24 weeks for re-treatment of chronic hepatitis C patients who failed to respond to interferon-alpha monotherapy in Taiwan. *Liver Int* 2004; **24**: 595–602.
6. McHutchison JG, Gordon SC, Schiff ER, *et al*. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. *N Engl J Med* 1998; **339**: 1485–92.
7. Fried MW. Side effects of therapy of hepatitis C and their management. *Hepatology* 2002; **36**(Suppl. 1): S237–44.
8. Van Gool AR, Kruit WH, Engels FK, Stoter G, Bannink M, Eggermont AM. Neuropychiatric side effects of interferon-alfa therapy. *Pharm World Sci* 2003; **25**: 11–20.
9. McHutchison JG, Manns M, Patel K, *et al*. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. *Gastroenterology* 2002; **123**: 1061–9.
10. Rifai MA, Bozorg B, Rosenstein DL. Interferon for hepatitis C patients with psychiatric disorders. *Am J Psychiatry* 2004; **161**: 2331–2.
11. Miyaoka H, Otsubo T, Kamijima K, Ishii M, Onuki M, Mitamura K. Depression from interferon therapy in patients with hepatitis C. *Am J Psychiatry* 1999; **156**: 1120.
12. Hauser P, Khosla J, Aurora H, *et al*. A prospective study of the incidence and open-label treatment of interferon-induced major depressive disorder in patients with hepatitis C. *Mol Psychiatry* 2002; **7**: 942–7.
13. Kraus MR, Schafer A, Faller H, Csef H, Scheurlen M. Psychiatric symptoms in patients with chronic hepatitis C receiving interferon alfa-2b therapy. *J Clin Psychiatry* 2003; **64**: 708–14.
14. Horikawa N, Yamazaki T, Izumi N, Uchihara M. Incidence and clinical course of major depression in patients with chronic hepatitis type C undergoing interferon-alpha therapy: a prospective study. *Gen Hosp Psychiatry* 2003; **25**: 34–8.
15. Koskinas J, Merkouraki P, Manesis E, Hadziyannis S. Assessment of depression in patients with chronic hepatitis: effect of interferon treatment. *Dig Dis* 2002; **20**: 284–8.
16. Bodenheimer HC Jr, Lindsay KL, Davis GL, Lewis JH, Thung SN, Seeff LB. Tolerance and efficacy of oral ribavirin treatment of chronic hepatitis C: a multicenter trial. *Hepatology* 1997; **26**: 473–7.
17. Raison CL, Borisov AS, Broadwell SD, *et al*. Depression during pegylated interferon-alpha plus ribavirin therapy: prevalence and prediction. *J Clin Psychiatry* 2005; **66**: 41–8.
18. Raber J, Koob GF, Bloom FE. Interferon-alpha and transforming growth factor-beta 1 regulate corticotrophin-releasing factor release from the amygdala: comparison

with the hypothalamic response. *Neurochem Int* 1997; **30**: 455–63.
19. Owens MJ, Nemeroff CB. The role of corticotrophin-releasing-factor in the pathophysiology of affective and anxiety disorders: Laboratory and clinical studies. *Ciba Found Symp* 1993; **172**: 296–308.
20. Dallman MF, Jones MT. Corticosteroid feedback control of ACTH secretion: effect of stress-induced corticosterone secretion on subsequent stress responses in the rat. *Endocrinology* 1973; **92**: 1367–75.
21. Lieb K, Engelbrecht MA, Gut O, *et al*. Cognitive impairment in patients with chronic hepatitis treated with interferon alpha (IFN-α): results from a prospective study. *Eur Psychiatry* 2006; **21**: 204–10.
22. Amorim P. Mini International Neuropsychiatric Interview (MINI): validation of a short structured diagnostic psychiatric interview. *Rev Bras Psiquiatr* 2000; **22**: 106–15.
23. Farber GA, Levin T, White CA. A cognitive therapy conceptualization of panic disorder exacerbated by interferon treatment. *Gen Hosp Psychiatry* 2005; **27**: 329–37.
24. Pariante C, Orru M, Baita A, Farci M, Carpiniello B. Treatment with interferon-[alpha] in patients with chronic hepatitis and mood or anxiety disorders. *Lancet* 1999; **354**: 131–2.
25. Renault PF, Hoofnagle JH, Park Y, *et al*. Psychiatric complications of long-term interferon alpha therapy. *Arch Intern Med* 1987; **147**: 1577–80.
26. Castera L, Zigante F, Bastie A, Buffet C, Dhumeaux D, Hardy P. Incidence of interferon alpha-induced depression in patients with chronic hepatitis C. *Hepatology* 2002; **35**: 978–9.
27. Mcdonald EM, Mann AH, Thomas HC. Interferons as mediators of psychiatric morbidity. An investigation in a trial of recombinant alpha-interferon in hepatitis-B carriers. *Lancet* 1987; **21**: 1175–8.
28. Parana R, Lyra L, Trepo C. Intravenous vitamin complexes used in sporting activities and transmission of HCV in Brazil. *Am J Gastroenterol* 1999; **94**: 857–8.
29. Conry-Cantilena C, Vanraden M, Gibble J, *et al*. Routes of infection, viremia, and liver disease in blood donors found to have hepatitis C virus infection. *N Engl J Med* 1996; **27**: 1691–6.
30. Johnson ME, Fisher DG, Fenaughty A, Theno SA. Hepatitis C virus and depression in drug users. *Am J Gastroenterol* 1998; **93**: 785–9.
31. Gohier B, Goeb JL, Rannou-Dubas K, Fouchard I, Cales P, Garre JB. Hepatitis C, alpha interferon, anxiety and depression disorders: a prospective study of 71 patients. *World J Biol Psychiatry* 2003; **4**: 115–8.
32. Schaefer M, Schwaiger M, Garkisch AS, *et al*. Prevention of interferon-alpha associated depression in psychiatric risk patients with chronic hepatitis C. *J Hepatol* 2005; **42**: 793–8.
33. Kraus MR, Schafer A, Al-Taie O, Scheurlen M. Prophylactic SSRI during interferon alpha re-therapy in patients with chronic hepatitis C and a history of interferon-induced depression. *J Viral Hepat* 2005; **12**: 96–100.
34. Capuron L, Ravaud A. Prediction of the depressive effects of interferon alpha therapy by the patient's initial affective state. *N Engl J Med* 1999; **29**: 1370.
35. Quarantini LC, Miranda-Scippa A, Schinoni MI, *et al*. Effect of amantadine on depressive symptoms in chronic hepatitis C patients treated with pegylated interferon: a randomized, controlled pilot study. *Clin Neuropharmacol* 2006; **29**: 138–43.
36. Quarantini LC, Miranda-Scippa A, Paraná R, Sampaio AS, Bressan RA. Acute dystonia after injection of pegylated interferon alpha-2b. *Mov Disord* 2007; **22**: 747–8.
37. Loftis JM, Hauser P. The phenomenology and treatment of interferon-induced depression. *J Affect Disord* 2004; **82**: 175–90.