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Subthreshold mania as predictor of depression during interferon treatment in HCV$^+$ patients without current or lifetime psychiatric disorders

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Abstract

Background: Depression is considered the most frequent interferon (IFN)-α-induced psychiatric disorder. However, other neuropsychiatric side effects of IFN treatment, such as irritability, anxiety, and manic episodes, are reported as well. We analyzed the impact of lifetime manic–hypomanic symptoms and anxiety on the development of depression in hepatitis-C-virus-infected subjects treated with two different types of IFN-α. **Methods:** At baseline, subjects received thorough diagnostic assessment to exclude lifetime or current psychiatric symptoms. During treatment, subjects were administered interviewer-based and self-report instruments. **Results:** Six (12%) of 49 individuals with a negative history of psychiatric disorders developed major depression during treatment with IFN. The onset of depression was significantly associated with the presence of lifetime subthreshold manic–hypomanic symptoms. Subjects exceeding manic threshold were more likely to develop depression than those below threshold (33.3% vs. 7.5%, P=.033). **Conclusions:** Our data suggest that individuals treated with IFN with no past history of psychiatric disorders are more likely to develop depression if they experienced subthreshold manic–hypomanic symptoms in their lifetime. These findings derive from an exploratory study and may have important implications for the prevention of IFN-induced depression if replicated in larger studies.

Keywords: Depression; Interferon treatment; Subthreshold mania; HCV$^+$ patients

Introduction

Evidence from a number of studies suggests that the incidence of neuropsychiatric side effects induced by interferon (IFN) treatment in hepatitis-C-virus (HCV)-infected patients ranges between 7% and 35% [1,2]. Variation in rates across studies depends on many factors, including treatment dosage, inclusion criteria, methods used to assess psychiatric side effects, and type of side effects considered. Despite these variations, there is a general consensus that IFN-induced depressive symptoms are the most common, with an estimated incidence of 23%. Recently, attention has been given to irritability, anxiety, and manic episodes during IFN treatment [3–6], suggesting that these symptoms are also important neuropsychiatric effects of this treatment. Several

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studies indicate that patients with a positive psychiatry history are more prone to developing psychiatric side effects during IFN treatment than those without [7,8]. Moreover, during the previous years, an increasing body of evidence suggests that the presence of subthreshold depressive symptoms before the initiation of IFN therapy is predictive of subsequent depression induced by IFN [9]. Conversely, no attention, to the best of our knowledge, has been given to the potential role of current or lifetime manic–hypomanic symptoms as predictors of depression during IFN treatment. Studies conducted in the general population and in clinical samples suggest the potential clinical significance of these symptoms. Judd and Akiskal [10], in a recent reanalysis of epidemiological catchment area data, have argued that subsyndromal manic symptoms are not 'benign' because they are associated with increased service use for mental health problems, need for welfare, and disability benefits. This view is also supported by Akiskal et al. [11], who found that, in a cohort of 559 depressed patients evaluated prospectively up to 11 years, the lifetime presence of soft bipolar temperamental dysregulations was predictive of more severe subsequent depressive episodes and switch to bipolar II disorder.

Instruments used to assess full-blown mania, such as the Bech–Rafaelsen Mania Scale (BRMAS) [12], are available in the literature. In addition to this scale, in the present study, we used the Mood Spectrum Self-Report (MOODS-SR), a broad assessment that includes typical and atypical symptoms of major depression and bipolar disorder; behavioral patterns and other features related to core symptoms that may either be prodromal precursor states or sequelae of a previously expressed disorder; and temperamental or personality traits [13]. Evidence on the clinical utility of mood spectrum assessment has already been provided by Cassano et al. [14], who found a significant relationship between the presence of lifetime manic–hypomanic symptoms and increased suicidal risk in patients with recurrent unipolar depression.

The aim of this prospective study is to determine whether a lifetime history of subthreshold mania constitutes a risk factor for depression during treatment with IFN in HCV-infected patients. The role of trait and state anxiety as a risk factor is also examined. Given that some authors have rightly pointed out that persons with hepatitis C come from population subgroups who carry a high risk of psychiatric disorders [15], we decided to select patients without a previous history of psychiatric disorders to test the hypothesis that subthreshold mania predicts IFN-induced depression.

Methods

Study population

For the purpose of this study, we analyzed data derived from a multicenter controlled pilot study on the comparative safety and tolerability of two types of IFN (unpublished data, available upon request).

Naïve patients with chronic HCV infection (Genotype 1, 2, or 3, classified according to Simmonds), of both genders, aged ≥18 years, and with a liver biopsy providing a histological diagnosis of active or persistent chronic hepatitis were screened in three academic Italian centers (Bologna, Pisa, and Naples) for potential participation in the trial.

Exclusion criteria were as follows: previous treatment with IFN-α or other antiviral agents; pregnancy or breastfeeding; current or lifetime psychiatric disorders; current or lifetime alcohol or substance use disorders; and positivity for anti-human immunodeficiency virus, hepatitis B surface antigen, anti-hepatitis delta virus, autoimmune hepatitis, liver cirrhosis, metabolic liver diseases, and neoplastic diseases. The study had been designed before pegylated IFN was made available on the Italian market. Eligible patients were randomized to: (a) alfaferone, 3 MU, tiw, sc, plus ribavirin (Rebetol), 1000–1200 mg/day, po (patients weighing ≤75 kg received 1000 mg daily as two 200-mg capsules in the morning and three 200-mg capsules in the evening; patients weighing >75 kg received 1200 mg daily as three 200-mg capsules in the morning and three 200-mg capsules in the evening); (b) intron-A (rIFN-α2b), 3 MU, tiw, sc, plus ribavirin (Rebetol), 1000–1200 mg/day, po (patients weighing ≤75 kg received 1000 mg daily as two 200-mg capsules in the morning and three 200-mg capsules in the evening; patients weighing >75 kg received 1200 mg daily as three 200-mg capsules in the morning and three 200-mg capsules in the evening).

Patients were stratified by genotype (Genotype 1/ Genotype 2 or 3).

The duration of treatment was 48 weeks for patients with Genotype 1 and 24 weeks for patients with Genotype 2 or 3. Patients with Genotype 1 who failed to show virological response after 6 months of treatment were discontinued from treatment. All responders participated in a 6-month follow-up period. Patients with Genotype 1 were assessed at baseline and monthly up to the 12th month of treatment, and patients with Genotypes 2 and 3 were assessed at baseline and monthly up to the sixth month of treatment. Psychiatric side effects of treatments were assessed by experienced psychiatrists, including one of the authors (L.M.).

Instruments

Psychiatric diagnostic assessment was conducted at baseline using the Structured Clinical Interview for DSM-IV for Axis I DSM-IV Disorders, patient edition (SCID-I/P, version 2.0) [16], to confirm the absence of any current or lifetime psychiatric disorders.

The following interview-based instruments were administered on scheduled assessments to detect changes in clinical condition and psychiatric side effects: the Brief Psychiatric Rating Scale (BPRS; version 4.0, 24 items) [17], the Clinical Global Impressions (CGI) scale [18], the