# Psychosis During Peginterferon-α2a and Ribavirin Therapy: Case Report

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**Pegylated Interferon-alpha, combined with ribavirin, gives high sustained virological response in patients with hepatitis C virus, an important public health problem and one of the most frequent chronic infectious diseases worldwide. Though it has therapeutic benefits, treatment with IFN-alpha may be complicated by various side effects, especially symptoms of major depression and acute mania. Psychosis is a rare side effect, and its management usually includes discontinuation of IFN-alpha. We report a case of psychotic disorder that occurred during therapy with pegylated Interferon-alpha given associated with ribavirin. After good response to psychiatric treatment, it became possible to finish the anti-viral therapy.**

**Key Words: Interferon-alpha, hepatitis C, psychosis.**

Infection with hepatitis C virus is an important public health problem and one of the most frequent chronic infectious diseases worldwide, with a global prevalence of 1%-2% [1]. Pegylated interferon-alpha (PEG-IFN), combined with ribavirin, give sustained virological response (complete eradication of hepatitis C virus and lack of hepatitis C viral load six months after interferon-alpha (IFN-alpha) treatment is completed) in 50%-59% of patients with genotype 1 and in 80%-90% of patients with genotypes 2 and 3 [2,3]. The new preparations of PEG-IFN, both alpha 2a and 2b, have an extended half-life and appear to increase sustained viral response rates, while offering the convenience of once-a-week dosing [4]. Despite its therapeutic benefits, treatment with IFN-alpha can be complicated by various side effects, especially symptoms of major depression and acute mania [5]. Psychosis is a rare side effect and its management usually includes IFN-alpha discontinuation [6]. According to expert consensus, patients with chronic hepatitis C should be treated with IFN plus ribavirin, regardless of psychiatric status. One unexplored point is how to manage serious mental disease, such as acute psychosis during treatment with IFN.

We report a case of psychotic disorder that occurred during therapy with PEG-IFN associated with ribavirin. Due to good response to psychiatric treatment, it became possible to complete anti-viral therapy.

## Case Report

Male, 48 years old, divorced, with a diagnosis of chronic hepatitis C, genotype 3, exposed to hepatitis C virus (HCV) about 25 years before, through injecting drugs. He had been treated, two years before, with conventional interferon, without clearance of HCV. During this period, he presented a setback of enraged behavior and suspiciousness, chronic symptoms that had been previously observed, as he was diagnosed as having a paranoid personality disturbance (APA-2000, DSM-IV-TR), although without psychotic symptoms.

He initiated re-treatment with, 180 μg pegylated interferon alpha 2-a per week plus 1,200 mg ribavirin /day. At the beginning of the second month of taking PEG-IFN, the patient, once more, presented symptoms that were similar to the ones he presented during the first anti-viral treatment, however they worsened rapidly; he manifested self-referred persecutory delusion, associated with aggressiveness. An evaluation by the psychiatric service was requested. The patient, despite his psychotic condition, was willing to use anti-psychotic drugs, in order to maintain the treatment with IFN-alpha, even though, he did not believe that he had any psychiatric disturbance. Risperidone at 2 mg/day was initiated. After a week, he was less anxious and less aggressive, in spite of still being in a psychotic condition. During the second week, he presented a significant improvement, but he still doubted the psychotic problems, although with some degree of insight. Within a month, the patient was free from delusion, back to his usual suspiciousness pattern. He had not been using injectable drugs for over 20 years and the family history did not reveal any cases of psychiatric disorders. The patient was able to complete the anti-viral treatment without IFN dose reduction and succesfull virological response.

## Discussion

There are limited reports describing how interferon-alpha can induce psychotic disorders. Some of them refer to patients with previous psychiatric disorders [6-8]. Tamam et al. reported a case of a youth, without any previously-proposed risk factor for developing psychiatric adverse effects, who developed persecutory delusions with auditory hallucinations, after five

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months on INF therapy for chronic hepatitis B. The symptoms persisted with only partial recovery even four months after discontinuation of IFN-alpha therapy and inclusion of antipsychotic drug treatment [9].

Several risk factors are thought to increase the probability of emergent psychiatric comorbidity during IFN-alpha treatment, including previous history of any psychiatric illness, a history of substance abuse, a family history of psychiatric illness and a history of suicidal ideas. Although these factors are not well validated, they have been used as exclusion criteria in several large chronic hepatitis C clinical trials [10]. The case presented above [9] suggests the possibility that a paranoid personality disorder can contribute to the occurrence of psychotic symptoms during treatment with IFN-alfa; however, we did not find any publications embracing this issue.

Challenging the widely-believed idea that a pre-existing psychiatric illness is a contraindication to the use of interferon, VanThiel et al. conducted a prospective study of patients with HCV and who had a documented psychiatric illness requiring use of psychotropic drugs. These patients received IFN-alpha therapy and were assessed by a psychiatrist once a month. Twenty-nine of the 31 patients completed IFN therapy, while two had exacerbated psychiatric illness during therapy; neither required hospitalization, leading the authors to conclude that patients with psychiatric illness and viral hepatitis can be treated successfully with interferon if they have appropriate psychiatric care [11].

There is another report of a young woman, with previous schizophrenic psychosis, who was treated with IFN plus ribavirin therapy for chronic aggressive hepatitis C. Her psychiatric status was monitored weekly and no psychotic or depressive signals developed during the 12 months of IFN therapy, during which the RNA of the virus C was undetectable [12].

There is evidence that IFN-alpha can decrease dopamine turnover in the striatum and increase release in cortical areas, a pattern that would partially explain the parkinsonian and psychotic symptoms that IFN induces. Shuto et al. and Raison et al. find that repeated administration of IFN-alpha inhibits dopaminergic neural activity in mice [13,14].

Some authors defend the hypothesis that IFN-alpha or viral infection could be involved in psychosis or schizophrenia pathogenesis. Zuckerman et al., based on findings that prenatal exposure to infection is associated with increased liability to schizophrenia, concluded that it is mediated by the maternal immune response, in particular, the pro-inflammatory cytokines released by the maternal immune system, which may disrupt fetal brain development [15].

High titers of IFN were found in the serum of 24.4% of patients with psychosis and in only 3.1% of control subjects. IFN-positive patients are more likely to have a recent onset or exacerbation of their illness and to be on low-dose medication [16].

The success in our case demonstrates the possibility of maintaining treatment with IFN-alpha in a patient who develops a psychotic disturbance during anti-viral therapy, provided that he receives adequate anti-psychotic therapy. Systematic studies would be useful to facilitate the detection and treatment of neuropsychiatric complications of IFN therapy.

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