

# Successful treatment of psychosis induced by interferon alpha and ribavirin with paliperidone: first case reported

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## ABSTRACT

Several clinical studies have shown a large number of mental symptoms by immunomodulatory treatment with interferon (IFN). The most frequently described symptoms are depression, suicidal behaviour, manic symptoms, anxiety, psychosis and delirium, associated with other non-specific symptoms such as fatigue, irritability, psychomotor retardation, decreased libido, insomnia, difficulty in concentration and attention. Having a history of mental disorder contraindicates the use of IFN- $\alpha$ . These adverse effects that affect the mental state appear usually at the beginning of the treatment (most after 3 weeks of treatment). The incidence of psychotic episodes is low and the episodes usually remit when treatment is interrupted; only some cases require antipsychotic treatment. We present the case of a patient affected with hepatitis C who began to present self-referential delirious symptoms after receiving the treatment with IFN and who was successfully treated with paliperidone. This patient could be classified within the group of high-risk psychiatric patients given the family history of schizophrenia and his personal history of illegal drug consumption. The pharmacological actions of paliperidone are similar to other high potency atypical antipsychotics. The receptor-binding profile of paliperidone most closely resembles that of risperidone and ziprasidone. Paliperidone differs from risperidone and most other antipsychotics by its relatively low extent of enzymatic hepatic metabolism. To the best of our knowledge, this is the first case described that was successfully treated with paliperidone.

## INTRODUCTION

Addictions and mental illness comorbidity are more frequent in patients with chronic hepatitis C than in the general population. In addition, the treatment with interferon alpha (IFN- $\alpha$ ) frequently results in psychiatric side effects, which are the risk factors for a failed treatment, leading to a major impact on the quality of life and reduction of therapeutic adherence.<sup>1,2</sup>

Pegylated antiviral therapies and high-standard IFN in combination with ribavirin are frequently associated with psychiatric side

effects, which can occur in 30%–80% of patients under treatment.<sup>3</sup>

Moderate depressive syndromes can appear in up to 70% of the cases and major depressive episodes around 15%–45%. Fatigue is the most prominent side effect, occurring in 80% of cases. Anger, irritability and/or hostility have been described in 50% of treated patients.<sup>2</sup> Alterations in sleep, anxiety, cognitive alterations can occur in 50% of cases. In contrast, mania and psychosis are very infrequent side effects, which can reach up to 3%. Finally, suicidal thoughts have been described in 10% of patients under treatment with IFN- $\alpha$ , with some cases of completed suicide.<sup>4</sup>

Specifically, ribavirin is known to cause haemolytic anaemia, while boceprevir is associated with irritability, insomnia, anaemia and dysgeusia.<sup>5</sup>

There are some other risk factors which need to be contemplated such as previous history of affective disorder, sleep disturbances, advanced age, organic brain alteration (vascular pathology, AIDS encephalopathy, etc), together with limited social and functional support.<sup>4</sup>

Paliperidone, which is pharmacologically identical to 9-hydroxyrisperidone, exhibits high affinities for dopamine type 2 and serotonin 5-hydroxytryptamine-2 receptors but does not undergo significant hepatic metabolism. The drug is well tolerated in patients with poor hepatic function and seems unlikely to be susceptible to metabolic drug interactions.<sup>6</sup>

## CASE REPORT

A 34-year-old man was referred to the mental health unit by the digestive system specialist. The patient presented psychotic symptoms

after the treatment for hepatitis C virus (HCV) infection with pegylated IFN- $\alpha$ -2b 3 MU, subcutaneously, 3 days a week and ribavirin in 200 mg oral tablets at a dose of 1000 mg/day for 3 weeks.

### Personal history

- ▶ Medical–surgical antecedents: chronic hepatopathy in cirrogenic evolution by HCV (genotype 1a).
- ▶ Illegal drugs: former illicit drug addict parenterally (heroin); former consumer of cocaine and cannabis. Follow-up by an illegal drug addiction centre since the age of 30.
- ▶ Psychiatric antecedents: self-limited cocaine induced psychosis, which did not require treatment.

### Family background

The patient's father had been diagnosed with non-specified psychosis, and his grandfather was diagnosed with schizophrenia.

### Current illness

After the first 3 weeks of the administration of antiretroviral treatment, the patient began to present behavioural changes and sleep–wake inversion coexisting with decreased sleep needs. He exhibited delusions of persecution and filiation (asserting that he was not the biological son of his mother). He also showed an unstructured religious mystical ideation (he believed that he was involved in some divine plans).

He presented intrusive and ego-dystonic obsessive ideas, which he recognised as not very rational and contained sexual contents towards his grandmother, but these were not accompanied by compulsive behaviours. These ideas generated great anguish. He exhibited hallucinations in the form of voices that he recognised as his father and a psychologist who attended him years ago. He presented soliloquies (he had conversations about his work, his life with these people). For this reason, antiretroviral treatment was withdrawn, despite not having complied with the 48 weeks recommended duration. Undetectable viral load was not accomplished either. He was immediately referred to the mental health unit.

### Physical examination

- ▶ Cardiopulmonary auscultation: within normality.
- ▶ Abdominal examination: hepatomegaly as the only remarkable finding

### Psychopathological exploration

He was presented as a middle-aged man, with a careful and suitable behavioural appearance. He was conscious and oriented, and he was approachable and collaborative.

There was a slight decrease in attention and concentration.

Immediate memory did not present alterations. There was an increase in speech pressure. He exhibited delusional ideation of prejudice, filiation and poorly structured religious mystic themes. The mood was hyperthymic, with restlessness and without respecting the interpersonal

distance, and slightly uninhibited. He exhibited auditory hallucinations in the second and third person and he displayed echo and thought phenomena. The patient verbalised obsessive ideas and delusional ideation of non-systematised persecution. There was no desire for death or tanatic ideation. He presented global insomnia and hyporexia. Null disease awareness at the moment.

### Supplementary tests

- ▶ Haemogram: haematies 4 950 000 mm<sup>3</sup>; haemoglobin 16.5 g/L; haematocrit 48.4%; mean corpuscular velocity 97.7 fL; mean corpuscular haemoglobin 33.4 pg; platelets 134x 10<sup>9</sup>/L; rest within normality.
- ▶ Biochemistry: aspartate transaminase 114 U/L; alanine aminotransferase 177 U/L; gamma-glutamyl transpeptidase 188 U/L.
- ▶ Thyroid stimulating hormone: 3.2 mIU/L; alfafeto-protein 2  $\mu$ g/L.
- ▶ Coagulation, lipid profile, vitamin B12 and folic acid: within normality.
- ▶ Serologies: syphilis, Borrelia, HIV, Epstein-Barr virus, cytomegalovirus and hepatitis B virus negative; positive HCV.
- ▶ Abdominal ultrasound: liver with a rough appearance, with somewhat irregular borders and left hepatic lobe enlarged, without space-occupying lesions; normal hepatopetal flow portal; rest without significant findings. The findings are suggestive of chronic hepatopathy in cirrogenic evolution.

### Diagnosis

In our case, we detected delusional ideation of harm, filiation and religious mysticism, as well as hallucinations in the second and third person. The conscience was not affected.

He was diagnosed as IFN-induced and rivabirin-induced psychosis following the criteria for the suspected diagnosis of psychosis by IFN- $\alpha$ :

- ▶ Start of symptoms before 3 weeks of treatment.
- ▶ Family history of mental disorder.
- ▶ Personal history of psychosis, affective disorder, alterations in sleep, advanced age, organic brain alteration, toxic consumption.
- ▶ Key symptoms such as delusional ideation, thought disorders, hallucinations or affective alterations.

### Evolution and treatment

The progressive increase of transaminases in the last 6 months required the choice of an antipsychotic avoiding hepatic metabolism. Paliperidone extended release (ER) is an atypical antipsychotic that, unlike other antipsychotics, is not extensively metabolised in the liver.<sup>7</sup> A pharmacokinetic analysis in patients with moderate hepatic impairment and healthy volunteers showed that unbound plasma concentrations of paliperidone ER were similar between the populations.<sup>8</sup> Consequently, no dose adjustment is required in patients with mild or moderate hepatic impairment.<sup>9</sup>

Different studies suggest that paliperidone is well tolerated in patients with schizophrenia or schizoaffective disorder who have a stable active hepatic disease.<sup>10</sup> Initially, he was treated with oral paliperidone in a dose of 6 mg/24 hours and it was switched to intramuscular paliperidone palmitate after 14 days due to the patient's very poor oral medication adherence and good response to oral paliperidone. The psychotic symptomatology diminished until it was encapsulated. Previous treatment with methadone at 40 mg was maintained.

The auditory hallucinations were translated in the chronic form but with very poor affective repercussion, except in moments of a lot of hallucinatory activities, in which the patient tended to isolate himself and he only responded to the auditory hallucinations that provoked him. These episodes lasted about 2 weeks and were resolved by temporarily increasing of the antipsychotic. The intercrisis periods lasted several months. The awareness of the disease had been increasing until the patient adequately criticised the psychotic symptoms, but the biographical rupture persisted after receiving antiretroviral treatment.

In the last 2 years, the progression of hepatopathy had produced asthenia and problems in the digestive sphere in the patient. He had a feeling of disability and incapacity with reactive hypotonia in this vital situation.

Currently, a treatment with paliperidone at a dose of 3 mg/day and methadone ratio of 40 mg/day is ongoing.

The hallucinatory activity is chronic, although with little emotional repercussion, it is prescribed in the low doses (3 mg) of maintenance for the control of the symptomatology.

## DISCUSSION

Approximately 13% of patients with HCV receiving treatment with IFN- $\alpha$  have neuropsychiatric symptoms such as depression, anxiety, suicidal ideation or psychosis; the latter is observed in 1% of the cases.<sup>1</sup> Among the most frequent psychotic symptoms are the presence of auditory hallucinations and delusions of persecution. These symptoms have been recognised as a valid reason to interrupt the treatment, but there are cases in which the symptoms do not stop after removing it, despite receiving antipsychotics, as is the case with our patient.<sup>2,3</sup>

There are several proposed biological mechanisms underlying this proinflammatory-induced neurodegenerative effect including upregulation of the central serotonin transporter molecular, a decrease in neurogenesis in brain-neuronal circuits regulating mood, changes in tryptophan metabolism via activation of the enzyme indoleamine-D-oxygenase, changes in central glutamate metabolism, activation of the hypothalamic-pituitary-adrenal axis and alteration in cellular apoptosis mechanisms. How these mechanisms may interact is not clearly understood.<sup>11</sup>

In addition to the genetic and environmental risk factors for psychosis that our patient presents, has been able to favour the appearance of this disorder.

Regarding prevention, it would be a contribution to include the high psychiatric risk as a special group and study subjects. These high-risk groups must have psychological and psychiatric support at different times of treatment. Future studies should demonstrate efficient and effective models for research and longitudinal monitoring during the course of treatment, to standardise intervention and treatment models, in addition to focusing on extending management including depressive syndrome, evaluating anxious disorders, management of anger and mania and designing a multidisciplinary strategy to reduce the deterioration of the quality of life of these patients.

This is a clear example of how we underestimated correct anamnesis before selecting the treatment.

So far, this is the first published case found in a review through the PubMed search engine of psychosis secondary to treatment with IFN, and successfully treated with paliperidone.

**Correction notice** This article has been corrected since it was first published. The lead author's name was incorrectly listed in the author biography. This has been amended.

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