

## INTERFERON-ALPHA INDUCED DEPRESSION IN A PATIENT WITH HEPATITIS C

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### INTRODUCTION

Chronic infection with the hepatitis C virus is a common and growing problem, often affecting persons with psychiatric and substance use problems. Neuropsychiatric symptoms are commonly associated with chronic hepatitis C virus infection, its sequelae, and its treatment. Interferon-alpha (IFN-alpha) treatment has been repeatedly shown to induce significant symptoms of depression in 20% to 50% of patients. Ribavirin has been reported to be associated with increased depression when used as a single agent for hepatitis C virus (HCV) infection. Combined with fatigue, these symptoms represent a primary cause of poor compliance and/or treatment discontinuation (Raison et al. 2005). According to Renault et al. (1987) 17% of patients with chronic viral hepatitis treated with a 4 to 12-month course of recombinant human IFN-alpha developed psychiatric side effects. The psychiatric side effects fell into three categories: an organic personality syndrome characterized by irritability and short temper; an organic affective syndrome marked by extreme emotional lability, depression, and tearfulness; and a delirium marked by clouding of consciousness, agitation, paranoia, and suicidal potential. These psychiatric side effects appeared after one to three months of therapy, usually improved within three to four days of decreasing the dose of IFN-alpha, and invariably resolved once therapy was stopped (Renault et al. 1987).

Newer, pegylated preparations of IFN-alpha have a longer half-life, require once-per-week dosing, and may be associated with reduced neuropsychiatric burden.

The underlying pathogenic mechanisms include various effects on neuroendocrine, cytokine and neurotransmitter systems. Induction of the cytokine network modulates the serotonergic system and that major depression is related to activation of the cytokine network and disturbances in the serotonergic metabolism. IFN-alpha is a cytokine released early in viral infection that has both antiviral and antiproliferative activities (Schaefer et al. 2002).

The enzyme indoleamine 2,3-dioxygenase (IDO), which converts tryptophan into kynurenine, may play an important role, first, because IDO activation leads to reduced levels of tryptophan, the precursor of serotonin (5-HT), and thus to reduced central 5-HT synthesis.

Second, kynurenine metabolites such as 3-hydroxykynurenine (3-OH-KYN) and quinolinic acid (QUIN) have toxic effects on brain function. 3-OH-KYN is able to produce oxidative stress by increasing the production of reactive oxygen species (ROS), and QUIN may produce overstimulation of hippocampal N-methyl-D-aspartate (NMDA) receptors, which leads to apoptosis and hippocampal atrophy. Both ROS overproduction and hippocampal atrophy caused by NMDA overstimulation have been associated with depression (Wichers et al. 2004). In neuroimaging studies, depression has been linked to decreased activation in the dorsolateral prefrontal cortex, a phenomenon that is also seen with IFN-alpha treatment (Matthews et al. 2004). The carriers of the epsilon 4 allele of the apolipoprotein E gene may be at increased risk of developing many neuropsychiatric symptoms during IFN-alpha treatment, including irritability, anxiety and depressive symptoms (Raison et al. 2005).

### CASE REPORT

We present a case of 33 years old male, formerly addicted to heroin for 12 years. He was diagnosed with Hepatitis C five years ago. After abstaining from drugs for two years an outpatient treatment with pegylated interferon was introduced. The patient had no history of psychiatric treatment. Two months after the IFN therapy started he presented with depressed mood, apathy, melancholy, social isolation tendencies and intention to stop taking interferon. He was referred to psychiatric evaluation and diagnosed with Major Depressive Disorder (MDD).

Depressive symptoms were evaluated according to DSM-V criteria for MDD. A Beck's Depression Inventory (BDI), 21-item self-evaluating scale for depression, was used on the first appointment and reviewed on the 2<sup>nd</sup>, 4<sup>th</sup> and 8<sup>th</sup> week of escitalopram therapy.

On the first appointment (BDI score 42) clinical presentation was dominated by irritability, anxiety, lack of will, insomnia, social withdrawal and isolation. Fatigue, psychomotor retardation, low appetite and insomnia that had been formerly present, were then more intense. The patient was depressed with pessimistic stands and negative anticipation of the future accom-

panied by nihilistic thoughts and sense of hopelessness. Concentration disturbances were also noticeable.

After the initial assessment, escitalopram was introduced with careful monitoring due to hepatic disease and possible side-effects (initial daily dose of 2.5 mg was increased to 5 mg one week after) and clonazepam (2 mg 3x1 tbl/d).

Two weeks after initiating escitalopram treatment (BDI score 39) the patient was more relaxed but other symptoms persisted. Escitalopram dose was then raised to 10 mg per day.

Four weeks after, we established a significant BDI score decrease (24) and the patient felt much better. His mood improved significantly, the anxiety reduced, though still followed by milder depressive nihilistic thoughts, concentration disturbances and fatigue.

Eight weeks after (BDI 18), a milder morning lethargy and lowered mood were still present but without depressive thoughts. Cognitive disturbances and fatigue were still present but less intense. Escitalopram therapy therefore continued while clonazepam dose gradually decreased.

A significant decrease in BDI score was established four weeks after escitalopram therapy was introduced without interrupting of IFN therapy.

## DISCUSSION

Based on DSM-V criteria, a depressive syndrome that occurs during IFN therapy is considered a substance-induced mood disorder.

Patients who developed IFN-induced MDD were on IFN therapy for an average of 12.1 weeks prior to the development of MDD (Hauser et al. 2002), and our patient manifested depressive symptoms after 8 weeks. Health care providers should follow IFN-treated HCV patients for the development of MDD, particularly between the 2<sup>nd</sup> and 5<sup>th</sup> months of IFN therapy (Hauser et al. 2002).

As Pavlović et al. (2011) presented, the various reasons for high rate of depression in chronic hepatitis C (CHC) patients were explained by either-biological factors (neurotoxicity of HCV and numerous changes in the cerebral metabolism) but also psycho-social factors such as reaction to unfavourable CHC prognosis, negative expectation of the outcome, insufficient information about the disease and stigmatization, etc. Our patient also had thoughts of interrupting the treatment while depressive symptoms occurred.

The treatment of the side effects with antidepressant, in particular escitalopram, would help avoid early dropouts from interferon therapy. Prompt use of escitalopram in our case provided effective control of major depression and other psychological symptoms.

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Prophylactic antidepressant treatment in patients with hepatitis C on antiviral therapy is not necessary, but rather monitoring for early symptoms and highly effective escitalopram treatment initiated promptly after the onset of clinically relevant depressive symptoms.

## CONCLUSION

Neuropsychiatric symptoms are widely reported in association with both hepatitis C and IFN-alpha treatment. Furthermore, hepatitis C disproportionately infects psychiatric patients. Fearing psychiatric vulnerability, practitioners may withhold IFN-alpha inappropriately. Failure to recognize these side effects quickly and to treat them with supportive therapy, antidepressants and modification of the dose of IFN-alpha could result in limitation of therapy and serious personal and interpersonal consequences. Patients must be monitored for signs of depression during IFN-alpha therapy and antidepressants commenced when indicated. The efficacy of prophylactic treatment for prevention of IFN-alpha induced depression need to be proven in future trials.

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