

Interferon-induced depression in chronic hepatitis C

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Since the success rate of the antiviral treatment of chronic hepatitis C (HCV) is increasing, the knowledge of side effects due to this therapy must also improve. Among these side effects, depression and other neuro-psychiatric symptoms are among the most important. It must be outlined that conditions may exist before treatment in relation to the viral infection. However, pegylated interferon (IFN) administration is associated with a huge increase in the importance and the incidence of neuro-psychiatric symptoms. This has led several experts to claim that antiviral therapy should not be given to HCV patients having psychiatric contraindications. This last assertion seems to be disproved on the basis of results of recent clinical trials using selective serotonin reuptake inhibitors (SSRI). Pathogenesis of these neuro-psychiatric symptoms, however, remains unknown although the impact of IFN on glucocorticoid receptors and on serotonin 1A receptors is privileged. In conclusion, advances in HCV antiviral therapy and the comprehension and subsequent treatment of side effects induced by this therapy should allow us to treat more patients with greater success.

Keywords: neuro-psychiatric conditions, antiviral treatment, serotonin

The success rate of antiviral treatment in chronic hepatitis C (HCV) has considerably increased during recent years.¹⁻³ The actual success rate in treatment-naïve patients (i.e. sustained viral eradication) varies between 45% and 95% and is partly dependent on viral genotype and viral load but also on drug adherence.¹⁻³ In this situation, drug adherence remains a difficult problem due to the number and the severity of side effects induced by antiviral therapy. Among the side effects induced by standard antiviral therapy combining pegylated interferon (IFN) and ribavirin, depression and other neuro-psychiatric symptoms are among the most important.

Before discussing the role of antiviral treatment in the occurrence of depression, it is important to outline that neuro-psychiatric symptoms are also present in relation to the viral infection independently of any treatment.⁴ Among patients infected with HCV, there may be major psychiatric co-morbidity, such as substance abuse and dependence. Despite this fact, several data also suggest that HCV infection can induce neuro-psychiatric symptoms directly or through asthenia and reduced quality of life. Pathogenesis of HCV-related neuro-psychiatric symptoms, however, remains poorly understood. As HCV belongs to a family of neurotropic viruses (e.g. tick-borne encephalitis), several authors have investigated the effects of HCV on the CNS.⁵⁻⁷ HCV RNA has been detected in CSF and brain tissue. Moreover, differences between patients with hepatitis B virus (HBV) and HCV were observed regarding cognitive dysfunction detected by P300 potentials and by proton magnetic resonance imaging and spectroscopy.⁶ In this last study, elevations in basal ganglia and

white matter choline/creatine ratios have been found in HCV patients compared with healthy volunteers and patients with HBV. Presently, it still remains unclear whether neuro-psychiatric symptoms observed in HCV patients are directly related to the presence of HCV in the brain or indirectly through a centrally mediated effect of cytokines.

Antiviral treatment and particularly IFN may induce an increase in the incidence of neuro-psychiatric symptoms observed in HCV patients.^{4,8,9} This induction is directly related to IFN treatment since neuro-psychiatric symptoms have been observed in patients treated with this drug for HBV and malignant melanoma. In HCV, the importance of the problem remains debated: 15-60% of the patients will present psychiatric side effects during IFN therapy.^{1,4,8,9} Moreover, different studies and consensus statements have claimed that antiviral therapy should be withheld in HCV patients having psychiatric conditions, including depression.^{4,8,9} In contrast to this last assertion, more recent studies have strongly suggested that pre-existing psychiatric disorders should no longer be considered as contraindications to antiviral treatment of HCV.¹⁰⁻¹³ The results of these recent studies must however be taken with caution as an interdisciplinary setting including hepatologists, psychiatrists and specialized nurses as well as administration of an antidepressant treatment has been put in place to obtain similar results in patients with pre-existing neuro-psychiatric symptoms in comparison with HCV patients without pre-existing symptoms.

With regard to the antidepressant treatment, selective serotonin reuptake inhibitors (SSRI) have been shown to be effective.¹⁰⁻¹² It

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has been demonstrated that in patients with pre-existing neuro-psychiatric symptoms the use of an SSRI is able to reduce the incidence of major depression in comparison with non-SSRI-treated patients. Prescription of an SSRI is now advocated in combination with antiviral therapy in HCV patients when early symptoms of depression or other neuro-psychiatric symptoms emerge. Practically, when the clinical diagnosis of depression has been reached, it is recommended to use different scales to assess depression in HCV patients on antiviral therapy. Among them, the Hamilton depression rate scale, the Montgomery-Asberg depression rating scale and the Beck depression inventory seem to be the most useful. In routine clinical practice, they permit the clinician to measure the degree of depression of the patient and thus to start an antidepressant treatment, to refer the patient to a psychiatrist and/or to stop the antiviral treatment.

It has also been suggested that SSRIs could be prescribed preemptively in all HCV patients before starting antiviral therapy. This attitude has been proposed in view of the elevated incidence of depression and other neuro-psychiatric symptoms induced by antiviral treatment in HCV patients with or without pre-existing neuro-psychiatric symptoms. This point of view must be investigated in the context of clinical trials to avoid potentially unnecessary exposure of patients to SSRI.

Regarding the use of other antidepressants in the context of antiviral therapy, data are very limited. Even if tricyclic antidepressants can be useful and effective in this situation, they are preferably avoided as they may induce sedation and cognitive side effects and will thus amplify these side effects linked to IFN therapy.^{4,9} Moreover, their use should be associated with drug monitoring, and they may induce cardiotoxicity and toxicity in overdose.

The mechanisms of IFN- α -induced depression remain poorly understood. Among the different hypotheses, the impact of IFN on glucocorticoid receptors (GR) and on serotonin 1A (5-HT) receptors seems to be important. These receptors are known to be implicated in mechanisms leading to depression.^{8,9,14–16} IFN administration significantly increases plasma ACTH, cortisol and interleukin-6 concentrations in patients who will develop depression. Also the reduction in serum 5-hydroxytryptophan (5-HTP) and serotonin levels is highly correlated to the degree of depression during IFN treatment. From a mechanistic point of view, these data are in favour of the use of SSRI in the treatment of IFN- α -induced depression as well as in their prophylactic use. Moreover, *in vitro* data reinforce this point of view by demonstrating that IFN down-regulated GR and 5-HTR1A levels in lymphoid and hepatic cell lines.¹⁷ This down-regulation is decreased by the addition of an SSRI. These *in vitro* data must however be confirmed in patients since relatively high concentrations of IFN and fluoxetine have been used. Not only could the magnitude of IFN concentration play a role in these results but the duration of exposure of the neural cells to the different drugs could also modify the observations made *in vitro*. It is well known that mechanisms of receptor activation are based on a dose-response curve: the observed effect of a drug is a function of its concentration in the receptor compartment. These drug-receptor interactions and elicited effects are not only true for IFN but also for SSRI. As antagonism between IFN and SSRI has been postulated, work has to be performed to elucidate the pattern of antagonism: simple competition, non-competitive antagonism, allosteric antagonism? The response to this question should allow

us to better prescribe SSRI in HCV patients receiving antiviral therapy.

Since the pharmacokinetic parameters of pegylated IFNs are different from those of standard IFN and since the time of depression occurrence and its duration seem to also differ between pegylated and standard IFN, it will be important to determine whether the *in vitro* mechanisms on GR and 5-HTR1A receptors also apply to pegylated IFN.^{12,18} Studies using cerebral PET scan, magnetic resonance spectroscopy and/or imaging should contribute to answering this question. An intriguing possibility would be the use of lymphocytes as an indirect predictor of IFN-induced depression if, as suggested, GR and 5-HTR1A receptors on these cells reflect the metabolic process in brain cells.¹⁹

Another interesting point of view, which has been recently described by Turner and Blackwell,²⁰ is the intriguing possibility that IFN not only increases serotonin reuptake but also decreases serotonin synthesis. The negative effect of IFN on serotonin synthesis remains putative. However, animal studies showing that IFN administration significantly reduces serotonin levels in different part of the CNS indirectly favour this hypothesis. This may explain why not all HCV patients treated with IFN respond to SSRIs, which only act by inhibiting serotonin reuptake. These authors advocate the concomitant administration of an SSRI and dietary supplement of 5-HTP, serotonin's immediate precursor, to normalize synaptic serotonin levels. Even if their hypothesis seems to be attractive, the combination of a drug and dietary supplement must be investigated through clinical studies as safety issues must be assessed before routine use of such a practice can be recommended.

Finally it must be outlined that antiviral therapy may also disturb thyroid function, which may contribute to the development or exacerbation of neuro-psychiatric symptoms. Thus thyroid function needs to be monitored during antiviral therapy in HCV patients.

In conclusion, we are now gaining insight into the treatment and the mechanisms involved in major depressive disorders induced by IFN. These advances should allow us to treat more patients even if caution about the potential severity of the symptoms must be taken into account in the follow-up of these patients on antiviral therapy.

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