

Neuropsychiatric Side-Effects of Interferon-Alpha Treatment: Pathophysiology and Therapeutic Options

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ABSTRACT

Interferon alpha (IFN- α) is the approved standard of care for chronic hepatitis C and B. Unfortunately, it has neuropsychiatric side-effects that have a major impact upon the quality of life and the drug adherence. The mechanism of IFN- α -induced behavioral changes is complex, involving interactions between the immune system, the endocrine system, the monoaminergic systems and the opioid receptors. Recent studies support the neurodegeneration hypothesis as a possible mechanism of IFN- α -induced depressive behavior.

Although a meta-analysis showed that antidepressant pretreatment effectively reduces the incidence and severity of depressive symptoms, irrespective of pre-existing psychiatric disorders, it is not approved for prophylactic use. The “on demand” treatment strategy is justified as the majority of patients have only mild depressive symptoms. Patients with risk factors for depression undergoing IFN- α therapy need to be regularly screened and followed-up by a psychiatric specialist.

Further studies should be conducted to show which therapy is the most appropriate to reduce the neuropsychiatric symptoms that are related to the use of IFN- α and to investigate the clinical significance of IFN- α -induced neurodegeneration.

Keywords: chronic hepatitis, interferon-alpha, neurodegeneration, neuropsychiatric symptoms, depression

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INTRODUCTION

Interferon alpha (IFN- α), an endogenous cytokine with antiviral and immunomodulatory effects, is the approved standard of care for chronic hepatitis C and B (EASL Clinical Practice Guidelines 2014; 2012). The antiviral treatment is promising as the sustained viral response varies between 35-50% (1), there is proof of histological improvement and the reduction of hepatic inflammation and fibrosis after IFN- α treatment is associated with a lower risk of hepatocarcinoma and a reduction of the progression rate to cirrhosis (2). The success rate of antiviral treatment however depends on the viral genotype and viral load, but also on the patient adherence to treatment (3). Among the side effects of IFN- α , the neuropsychiatric symptoms have a major impact upon the quality of life and the drug adherence. The neuropsychiatric side effects may include minor symptoms, frequently ignored by the physician, such as fatigue, irritability, agitation and sleep disturbances ("neurovegetative symptoms") and major symptoms comprising depression and cognitive impairment (4). Moreover, in patients with hepatitis C virus infection, it is not always an easy task to distinguish among the effects of the viral infection itself and the treatment-induced symptoms, as the virus has brain tropism and even untreated patients may present with neuropsychiatric symptoms (5).

Pathophysiology

The biological mechanism of IFN- α -induced behavioral changes is not yet fully understood. It seems that the central role is played by the interaction between the immune system, the endocrine system, the serotonergic system and the opioid receptors.

Endocrine and immune mechanisms

Exaggerated hypothalamic-pituitary-adrenal (HPA) axis responses have been associated with depression during IFN-alpha therapy, suggesting that sensitized neuroendocrine responses, including corticotropin-releasing hormone (CRH), may represent a vulnerable pathway to IFN-alpha-induced neuropsychiatric symptoms (6). And although IFN- α causes marked activation of the HPA axis when administered acutely (7), significant adaptation of the HPA axis occurs following chronic IFN- α treatment, the latter being associated with flattening of the diurnal

cortisol rhythm and an increase in vesperal cortisol plasma concentrations, changes that significantly correlate with IFN- α -induced increases in depression scores and fatigue, as observed by Raison CL et al (Mol Psychiatry, 2010).

On the other hand, IFN- α is a potent activator of the inflammatory cytokine network. The activation of type I-IFN receptors induces the transcription of IFN-stimulated genes and thus the synthesis of IFN-induced 15 kDa protein, ubiquitin-specific proteinase 18 and guanylate-binding protein 3, all of them with cytokine-like properties (8). Moreover, IFN- α stimulates, in cell-cultures and in vivo, the expression of interleukin 1 (IL1), interleukin 6 (IL6), and tumor necrosis factor alpha (TNF- α) (9). All these proinflammatory cytokines (IFN- α , IL1, IL6 and TNF- α) have proved to modulate mood, behavior and sleep-wake cycle in animal models and in humans. They induce depressive-like symptoms, also known as "sickness" behavior in animal models (10), and also increase slow wave sleep duration (11).

The immune activation further induces cyclooxygenase-2 (COX-2) gene expression and prostaglandin E2 (PGE2) synthesis (12). The prostaglandin acts as a modulator of the sickness behavior syndrome and induces fever via hypothalamic EP3 receptor activation (13).

Opioid-receptors

IFN- α may also increase PGE2 brain levels by activating the μ -opioid receptors. In an animal model, Blalock JE et al (Biochem.Biophys. Res.Commu, 1981) showed that human IFN- α binds to brain opioid receptors with high affinity and produce analgesia. Furthermore, Wang YX et al (J. Neuroimmunology, 2004) demonstrated that the pyrogenic effect of IFN- α and PGE2 production induced by IFN- α administration in rodents are blocked by naloxone, a selective μ -opioid receptor antagonist, suggesting that fever of recombinant human IFN- α is mediated by IFN- α -opioid domain interaction with opioid receptor inducing prostaglandin E2 synthesis. Another effect of IFN- α which seems to be the result of μ -opioid receptors activation is the enhancement of slow-wave activity on electroencephalogram (EEG) in rabbits (14), electric phenomena described also in clinical trials in patients who developed psychosis during IFN- α therapy, by Suter CC et al (Mayo Clin. Proc, 1984). The diffuse slowing of EEG during IFN- α treatment in patients with chron-

ic hepatitis C was also associated with alteration of the mini-mental state examination results, as described by Kamei S et al (Eur Neurol, 2002).

In the animal models of IFN- α -induced depression, Makino M et al. (Br J Pharmacol, 2000) proved that the depressive-like behavior assessed as the time spent immobile in the forced swimming test was mediated by cerebral μ -opioid receptors, although the role of central opioid system in the occurrence of endogenous depression is not yet defined in human studies.

Monoamines

Proinflammatory cytokines and others proinflammatory molecules such as PGE2 activate also indolamine 2,3-dioxygenase (IDO), an enzyme involved in tryptophan catabolism, located in nonhepatic organs throughout the body (15). Tryptophan is the precursor of serotonin; low plasma levels of tryptophan may impair peripheral and cerebral serotonin synthesis (16). Tryptophan depletion may be due both to reduced food intake – a direct effect of IFN- α on hypothalamic glucose-sensitive excitatory neurons (17), and to increased catabolism of tryptophan by IDO activity enhancement. Also, in several clinical trials, Russo S et al (Psychosom. Med., 2005) and Capuron L et al (Biol Psychiatry, 2003) demonstrated that during IFN- α treatment, the decreased plasma levels of tryptophan have been associated with irritability and depression. As a matter of fact, Tsao CW et al (J Psychopharmacol., 2008) propose a secondary mechanism associated with the changes in serotonin metabolism described above, showing that in vitro, IFN- α induces serotonin uptake by increased serotonin transporter synthesis. This is demonstrated by the fact that fluoxetine, a selective serotonin reuptake inhibitor (SSRI), and celecoxib, a COX-2 selective blocker, both inhibit the IFN- α -induced serotonin uptake in cell cultures, as shown by Su HC et al (Int Immunopharmacol., 2011). It is well known the link between serotonin depletion, impaired serotonergic neurotransmission and endogenous depression, mechanism justifying the use of SSRI as antidepressants in clinical practice.

Shuto H et al (Brain Res., 1997) demonstrated that chronic IFN- α administration inhibits also the dopaminergic neural activity and metabolism in mice as measured in whole brain homogenates, excluding the cerebellum.

Furthermore, Sunami M et al (Clin. Neuropharmacol., 2000) described Parkinson-like motor disorders in patients treated with low doses of IFN- α for chronic hepatitis C.

Neurodegeneration hypothesis

In the last 20 years there has been an important shift in the understanding of the role of chronic inflammation and neurodegeneration in depression (18). There exists a substantial body of evidence that pleads for the association between an increase in proinflammatory cytokines and neurodegeneration. The enhancement of IDO activity leads to increased tryptophan catabolism via kynurenine pathway and an imbalance between its neurotoxic and neuroprotective end-products (19). 3-Hydroxykynurenine (3-OH-KYN) is one of the neurotoxic metabolites that initiates neuronal apoptosis by inducing reactive oxygen species production (20). Behan WM et al (Br J Pharmacol., 1999) suggested that quinolinic acid (QUIN), a potent N-methyl-D-aspartate (NMDA) receptor agonist, may mediate neuronal excitotoxicity during inflammation. Kynurenine acid is a NMDA-receptor antagonist and thus serves as a neuroprotective agent (21). IFN- α treatment in hepatitis C patients significantly increases the kynurenine/tryptophan ratio, reflecting IDO activity, and shifts the neurotoxic/neuroprotective balance towards a higher neurotoxic challenge (22). In animal models, Ishikawa J et al (Neuroreport, 2007) showed that long-term administration of IFN- α reduces the density of serotonergic and noradrenergic axons in the prefrontal cortex. Moreover, Hochstrasser T et al (Neuroscience, 2011) proved in brain organotypic slices, that inflammatory stimuli induced IDO expression and reduced survival of serotonergic neurons.

The kynurenine pathway is not the only mechanism that seems to be involved in the neurodegeneration-depression process induced by chronic inflammation. In another animal study, Ping F et al (Neurosci Lett., 2012) showed that repeated administration of IFN- α induces depressive-like behavior via down-regulation of the serotonergic receptor 5-HT1A and apoptosis in the hippocampus of mice brain. In addition to these mechanisms, the IFN-stimulated gene products may be directly involved in the apoptotic process, such as TNF- α -related apoptosis-inducing ligand, caspase-4, caspase-8, or death activating protein kinases (23).

Management of IFN- α -induced neuropsychiatric symptoms

In the majority of chronic hepatitis C virus patients, IFN- α treatment induces mild depressive symptoms (subthreshold depressive symptoms), including here anxiety, irritability, sleep disturbances, fatigue, low mood, loss of appetite, and only rarely severe signs and symptoms, suicidal ideation, social withdrawal, or anhedonia (24). Some patients may be at an increased risk for IFN- α -induced depression, such as those having pretreatment depressive symptoms or a history of major depression (4), poor sleep quality prior to IFN- α treatment (insomnia) (25), increased IL6 levels during antiviral treatment (26), polymorphism of serotonin reuptake transporter (27), or hyperactive stress response in the HPA axis after the first IFN- α dose administration (6). In addition, treatment risk factors include the dosage and the duration of IFN- α exposure, the neuropsychiatric adverse events increasing with higher doses and prolonged treatment (4).

A few prophylactic trials using SSRIs have been performed, suggesting that preventive treatment with SSRIs may be useful in patients receiving IFN- α therapy (28). However, in another prospective controlled trial, Morasco BJ et al (*J Affect Dis.*, 2007) showed no significant benefits for prophylactic treatment with SSRIs in patients on IFN- α antiviral treatment for chronic hepatitis C virus. The meta-analysis of the prospective controlled trials, done by Sarkar S et al (*Psychosomatics*, 2013), showed that antidepressant pretreatment effectively reduces the incidence and severity of depressive symptoms, irrespective of pre-existing psychiatric disorders, for both type of patients, either with melanoma or chronic hepatitis C infection. Still, antidepressants are not approved for prophylactic use in all patients and the "on demand" treatment strategy is justified as the majority of patients have only mild depressive symptoms and just a small percentage of patients receiving IFN- α develop major depression (29).

A promising alternative to SSRI prophylaxis is represented by the omega-3 polyunsaturated fatty acids, the recent study of Su KP et al (*Biol Psychiatry*, 2014) showing that 2 weeks of administration of eicosapentaenoic acid seems to be effective in the prevention of depression in hepatitis C virus patients receiving IFN- α therapy. However, more studies are needed.

The current recommendations are to associate the antidepressant treatment to antiviral therapy only if depressive symptoms appear during IFN- α administration and in this regard SSRI (citalopram and paroxetine) are considered the first choice, as proved by previous studies (4), patients being able to be effectively treated without the need to stop IFN- α therapy (30). The antiviral therapy should be suspended (until the depressive symptoms are adequately controlled) only in patients with severe depression, significant suicidal ideation, failure integrating in their work environment or disruption of family relationships (4). However, the diagnosis of an acute depressive episode during IFN treatment is often overlooked as these patients are primarily seen by their hepatologist and are not regularly screened and followed up by a psychiatric specialist (31). It's worth mentioning that Capouron L et al (*Biol Psychiatry*, 2004) found that symptoms of depression, anxiety and cognitive dysfunction were more likely to improve, whereas symptoms of fatigue, psychomotor slowing, altered sleep and anorexia were less responsive to paroxetine treatment.

On the other hand, in the presence of significant depression-related neurovegetative symptoms (fatigue, anorexia), without other symptoms related to depression, patients may be treated with agents modulating catecholaminergic neurotransmission, such as serotonin-noradrenaline antidepressants, bupropion or modafinil (4).

We must emphasize the limitation of IFN- α -induced depression in animal models (rats or mice) using human IFN, as there is a relatively low similarity between human and rodent type I IFN receptors (40-50% identity) (32). There are also studies providing evidence for significant species differences in opioid receptor-mediated modulation of noradrenergic and serotonergic-release in human as compared to rat neocortex (33). Therefore, although μ -opioid receptors seem to play a role in depressive behavior in rats, further studies are necessary to clarify their significance in humans.

Another therapeutic target could be the IDO enzyme and the neurotoxic metabolites of kynurenin-pathway. Salzberg-Brenhouse HC et al (*The Journal of Pharmacology and Experimental Therapeutics*, 2003) and McGeer PL et al (*Neurology*, 1996) showed that COX-2 or COX-1,2 inhibitors provide structural and func-

tional protection against quinolinic acid-induced neurodegeneration, both in animal models and clinical trials of Alzheimer disease in humans. Non-steroidal anti-inflammatory drugs (NSAIDs) are known to counteract a number of IFN- α -induced side effects, including flu-like syndrome, pro-inflammatory cytokine activation and stress hormone release. It is thus raised the possibility that NSAIDs could be used for the prevention of IFN- α -induced depression, given their attenuation of IFN- α induced alterations in monoamine turnover in prefrontal cortex and hippocampus, brain areas important in depression, in rodents (34). This could be important in practice, as Hadziyannis SJ et al (Gut, 2000) suggested that NSAIDs could potentiate the action of IFN- α in hepatitis C virus infection, increasing the sustained virological response rate. $\square$

CONCLUSIONS

So far it seems that the central physiopathologic mechanisms in IFN- α -induced behavioral changes is played by the interaction between the immune system, the endocrine

system, the serotonergic system and the opioid receptors.

Patients with risk factors for depression undergoing IFN- α therapy need to be regularly screened and followed-up by a psychiatric specialist, in order to find the appropriate timing of antidepressant treatment, to improve their quality of life and to reduce the risk of treatment discontinuation. Due to the limitations given by the use of animal models and the small clinical trials, further studies are needed to demonstrate which classes of drugs are more likely to improve the neuropsychiatric symptoms that are induced by IFN- α therapy. Along with that, long-term survey studies are also necessary to evaluate the clinical significance of IFN- α -induced neurodegeneration. $\square$

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