Interferon-induced depression: mechanisms and management

Interferon-alpha therapy in cancer or hepatitis C infection is significantly associated with depression. Interferon-alpha can enhance tryptophan metabolism leading to reductions in serotonin and accumulation of toxic kynurenine metabolites. Antidepressants may be effective as prophylaxis in patients with risk factors.

Cytokines are low molecular weight proteins that help to regulate haemopoiesis and immune responses. Examples of cytokines include the interleukins (IL), the interferons (IFN) and tumour necrosis factors. They may be up-regulated after an infection and can be associated with a number of 'sickness behaviours'. Similarly, clinical treatment of patients with cancer or chronic hepatitis C with cytokines such as interferon-alpha (IFN-α) has been associated with sickness behaviours. These include symptoms such as depression, irritability, impaired memory, insomnia, loss of appetite and asthenia (Schiepers et al, 2005). Some of these symptoms are similar to those seen in major depressive disorder. For example, major depressive disorder may present with depressed mood or anhedonia (loss of pleasure in usual interests) and other symptoms such as a persistent change in appetite or weight, psychomotor changes (retardation or agitation), insomnia or excessive sleep, guilt and worthlessness, poor concentration or indecision, and suicidal ideas or suicidal attempts (Mann, 2005). In at least one study about half of the patients on IFN-α became depressed and then improved on cessation of cytokine treatment. The risk of cytokine-induced depression is reduced and may be effectively prevented with the use of antidepressant drugs (Capuron and Miller, 2004).

IFN therapy and depression

IFNs are cytokines that are involved in host defence systems and help to modulate immune responses. IFN therapy is increasingly used to treat a number of malignancies, multiple sclerosis and chronic hepatitis C infection. However, preparations of IFN-α can induce neuropsychiatric adverse reactions. An early and rapid adverse effect after the use of high doses of IFN-α is that of a delirium. Mood disturbances such as depression and mania may also be observed. If present manic symptoms present with agitation and irritability; however depression is more common. IFN-α therapy can induce depression in chronic hepatitis C, chronic myelogenous leukaemia, melanoma and renal cell carcinoma (Raison et al, 2006). Up to about 60% of patients on IFN-α treatment can have significant depressive symptoms and about 30% of patients who receive IFN-α as a treatment for chronic hepatitis C may develop major depressive disorder during their course of treatment (Capuron and Dantzer, 2003). IFNs can also affect the haematological system and thyroid function. In fact, the combination therapy of pegylated IFN-α and the purine nucleoside analogue ribavirin may result in an anaemia-induced depression that is responsive to erythropoietin treatment. In addition, hypothyroid-induced depression demands that thyroid function is monitored (Asnis and De La Garza, 2005). Nevertheless, IFN-α-induced depression may present with two overlapping syndromes. An early neurovegetative syndrome that presents with anorexia, pain, lethargy and psychomotor retardation tends to appear within the first 2 weeks of IFN therapy, and is not very responsive to selective serotonin-reuptake inhibitors (SSRIs). A later depression-specific syndrome that is more responsive to SSRIs may develop over a period of weeks to months with disturbances in mood, anxiety and cognition (*Table 1*) (Capuron and Dantzer, 2003).

Risk factors

IFN-α-induced depression is more likely to occur in female subjects and in those with higher pre-treatment scores on the Beck depression inventory (Capuron et al, 2002). In addition, a family history of depression and advancing age are further risk factors. A small cohort of patients with chronic hepatitis C and without baseline psychiatric disorder underwent treatment with IFN-α-ribavirine combination therapy. Here higher baseline levels of immune activation, such as increases in soluble IL-2 receptor (sIL-2R), and IL-6 concentrations before

Table 1. Neuropsychiatric symptoms after interferon-alpha therapy

Delirium	
Manic irritability and agitation	
Depression	Early neurovegetative syndrome – anorexia, pain, lethargy and psychomotor retardation (little response to antidepressants)
	Later mood/cognitive syndrome – depressed mood, anxiety and cognitive dysfunction (responsive to antidepressants)

Dr Sepehr Hafizi *is Specialist Registrar in General Adult Psychiatry and* **Dr Elisa Favaron** *is Clinical Lecturer in General Adult Psychiatry at the University Department of Psychiatry, Warneford Hospital, Headington, Oxford OX3 7JX*

Correspondence to: Dr S Hafizi

exposure to IFN-α, were associated with increased incidence of subsequent major depressive disorder (Schiepers et al, 2005). However, there is little reliable evidence for an association between the number of previous episodes of depression and IFN-α associated depression (Capuron et al, 2002). Furthermore, with the high levels of psychopathology in chronic hepatitis C patients, future studies should ideally include a chronic hepatitis C control group that is not receiving IFN-α therapy.

How might IFN-α cause depression?

IFN-α may affect the expression of other cytokines and induce some of its effects indirectly. For example, significant relationships have been found between IFN-α-induced increases in IL-6 and IL-8 and depression scores in chronic hepatitis C patients (Bonaccorso et al, 2001). Also, interestingly IFN-α can lead to a release of serotonin (5-hydroxytryptamine; 5-HT) and catecholamines via IL-1β, which might explain the early mood lift seen in some patients with IFN-α therapy before emergence of depressive symptoms. However, chronic IFN treatment has been found to significantly reduce plasma 5-HT levels. In addition, IFN-α can increase serotonin reuptake transporter mRNA levels and decrease 5-HT1A receptor mRNA levels (Cai et al, 2005). However, the side effects of IFN therapy may also be significantly related to increased tryptophan catabolism.

The effects of IFN-α on tryptophan metabolism

The essential amino acid L-tryptophan is obtained from the diet and is metabolized via three pathways. Tryptophan is either incorporated into tissue protein, converted to 5-HT or is ultimately catabolized to carbon dioxide and water. About 1% of tryptophan is converted to 5-HT via the production of 5-hydroxytryptophan (5-HTP). At the blood–brain barrier, tryptophan is transported into the brain via a high affinity transporter system and here it competes with large neutral amino acids such as leucine, isoleucine, phenylalanine, threonine, tyrosine and valine.

About 99% of dietary tryptophan is catabolized by tryptophan (2,3)-dioxygenase (TDO) and indoleamine (2,3)-dioxygenase (IDO) via the kynurenine pathway. TDO and IDO catalyze tryptophan into N-formylkynurenine which then deformylates to kynurenine. Metabolism by IDO also produces the by-products 3-hydroxyanthranilic acid, picolinic acid and quinolinic acid. The end-products of this pathway also include nicotinic acid and nicotinamide adenine dinucleotides. TDO is found in the liver and is upregulated by corticosteroids, while IDO is expressed primarily in monocytes, macrophages and dendritic cells and is induced by pro-inflammatory cytokines such as IFN-α. Thus IFN-α therapy can lead to increased tryptophan degradation. This would result in an increase in the kynurenine:tryptophan ratio. Increased levels of the macrophage activation marker, neopterin would indicate that the enhanced tryptophan degradation is the result of immune activation and IDO activity in macrophages rather than of TDO activation (Frick et al, 2004). Accelerated tryptophan degradation can have deleterious effects. These include immunodeficiency, anaemia, cachexia and mood changes (Frick et al, 2004). The latter may be the result of a reduction in the biosynthesis of 5-HTP and 5-HT as these latter compounds, in addition to tryptophan, also serve as a substrate for IDO.

Patients who developed depressive symptoms while receiving IFN-α were shown to exhibit a greater reduction in their serum tryptophan levels. In particular, IFN treatment of chronic hepatitis C patients was associated with a decrease in tryptophan concentrations and an increase in kynurenine concentrations in plasma (Bonaccorso et al, 2002), while IFN therapy in melanoma patients who developed major depressive disorder was associated with greater increases in kynurenine and neopterin and more prolonged decreases in tryptophan. The decreases in tryptophan levels were positively correlated with depressive and anxiety symptoms (Capuron and Dantzer, 2003).

Neurotoxicity

More recently, it has been postulated that IFN-α-associated depression may be caused by immune-induced neurotoxic substances (Schiepers et al, 2005) and that some of the persistent cognitive side effects of IFN therapy in advanced human immunodeficiency virus (HIV) infection may be related to accumulation of quinolinic acid (Meyers et al, 1991). Cytokine-induced depression has been shown to correlate with kynurenine levels in some patients (Bonaccorso et al, 2002). Increases in kynurenine, 3-hydroxy-kynurenine (3-OH-KYN) and quinolinic acid might contribute to the development of depressive symptoms.

Peripheral kynurenine can cross the blood–brain barrier via a carrier and enter the brain where it is further metabolized in microglia, and 3-OH-KYN can induce oxidative stress via formation of free radicals and induce apoptosis (Schiepers et al, 2005). Furthermore, quinolinic acid causes neuronal death upon direct intra-cerebral injection in vivo and upon in vitro application to neuronal cultures (Takikawa, 2005). Following acute systemic activation of IDO, increased levels of quinolinic acid have been found in the plasma and CSF of gerbils (Saito et al, 1993). Increased quinolinic acid production may lead to excessive glutamatergic stimulation via agonistic actions at a subpopulation of hippocampal N-methyl-D-aspartic acid (NMDA) receptors and via oxygen radicals with consequent neurotoxicity. These metabolites may also cause hippocampal atrophy via glutamatergic excitation leading to a loss of corticosteroid receptors and interference in the negative feedback of the HPA axis. Increasing concentrations of quinolinic acid also overwhelm the protective effect of another metabolite of kynurenine, namely kynurenic acid. In fact, IFN-α treatment not only activates IDO, but also

increases the kynurenine:kynurenic acid ratio. This increase has been shown to correlate with Montgomery Asberg depression scale scores (Schiepers et al, 2005).

Hypothalamic–pituitary–adrenal axis

Many observations have reported a link between major depressive disorder and hypothalamic–pituitary–adrenal (HPA) axis dysfunction. In addition, cytokines such as IFN-α therapy have been associated with depressive symptoms and a hyperactive HPA axis (Capuron and Dantzer, 2003). In a study of patients with melanoma undergoing treatment with IFN-α, those patients who developed depressive symptoms also showed an exaggerated HPA axis response as revealed by increased adrenocorticotropic hormone and cortisol levels in response to IFN-α (Capuron et al, 2003). Furthermore, IFN-α activates other cytokines including IL-6, the levels of which has been found to correlate with the development of depressive symptoms and with adrenocorticotropic hormone and cortisol (Bonaccorso et al, 2001).

Cyclooxygenase-2

The enzyme cyclooxygenase (COX) helps to convert arachidonic acid to prostaglandins. It is present as three different isozymes: COX-1, COX-2 and COX-3. COX-2 in particular is involved with injury and inflammatory processes. In fact, systemic cytokines can activate COX-2 in CNS vascular endothelial cells and increase the expression of prostaglandins which can then diffuse into the brain and stimulate nearby neurons. COX-2 inhibitors can reduce the production of prostaglandins and pro-inflammatory cytokines. Interestingly, the COX-2 inhibitor rofecoxib has been shown to reduce depressive symptoms in a percentage of patients with osteoarthritis and co-morbid depression (Collantes-Estevez and Fernandez-Perez, 2003). In a prospective, double blind add-on study with reboxetine, 400 mg of the COX-2 inhibitor celecoxib produced reductions in the symptoms of depression additional to reboxetine in acutely depressed patients with major depressive disorder (Linthorst et al, 1995). In addition, COX-2 inhibitors are thought to influence the CNS 5-HT system either directly or indirectly via CNS-immune mechanisms. However, there have been questions regarding the cardiovascular safety of COX-2 inhibitors, and rofecoxib was withdrawn recently for this reason.

Management

It is important to first rule out depression caused by IFN-induced anaemia or thyroid dysfunction. If present these can be treated with erythropoietin or thyroxine supplements respectively. With respect to antidepressants a number of open trials and case reports have shown SSRIs and tricyclic antidepressants to be effective in the treatment of IFN-α-induced depression (Angelino and Treisman, 2005). However, there have not been any randomized controlled trials of antidepressants for the treatment of IFN-α-induced depression. Nevertheless, the use of antidepressants as prophylaxis before IFN therapy has been studied. In fact in a randomized controlled trial, paroxetine was found to be superior to placebo in the prevention of major depressive disorder in patients with melanoma when started 2 weeks before initiation of therapy with IFN and when continued for 12 weeks during the course of IFN therapy (Musselman et al, 2001). Additionally, other studies have also indicated a benefit in starting antidepressants in patients with current symptoms of depression before therapy with IFN-α has begun (Capuron et al, 2002).

The choice of an antidepressant for the unlicensed treatment of IFN-α-induced depression will depend upon tolerability, drug–drug interactions, concomitant physical illness and the presence of specific symptoms. If liver disease is present, however, slower titration is recommended. SSRIs are particularly useful as they can reduce irritability and anger. However, SSRIs are associated with increased bleeding tendencies, which together with concomitant non-steroidal anti-inflammatory drugs may increase the risk of IFN-related retinal haemorrhages. In addition, SSRIs can precipitate mania in vulnerable individuals, although this is less likely with paroxetine. Mirtazapine is a better choice if sexual dysfunction, insomnia, nausea or anorexia is a problem. Duloxetine, which potentiates both 5-HT and noradrenaline, is particularly helpful if somatic pain is present. Drug–drug interactions tend to occur if there is concurrent treatment with protease inhibitors for HIV infection. This is because protease inhibitors can affect the liver microsomal system (Asnis and De La Garza, 2005).

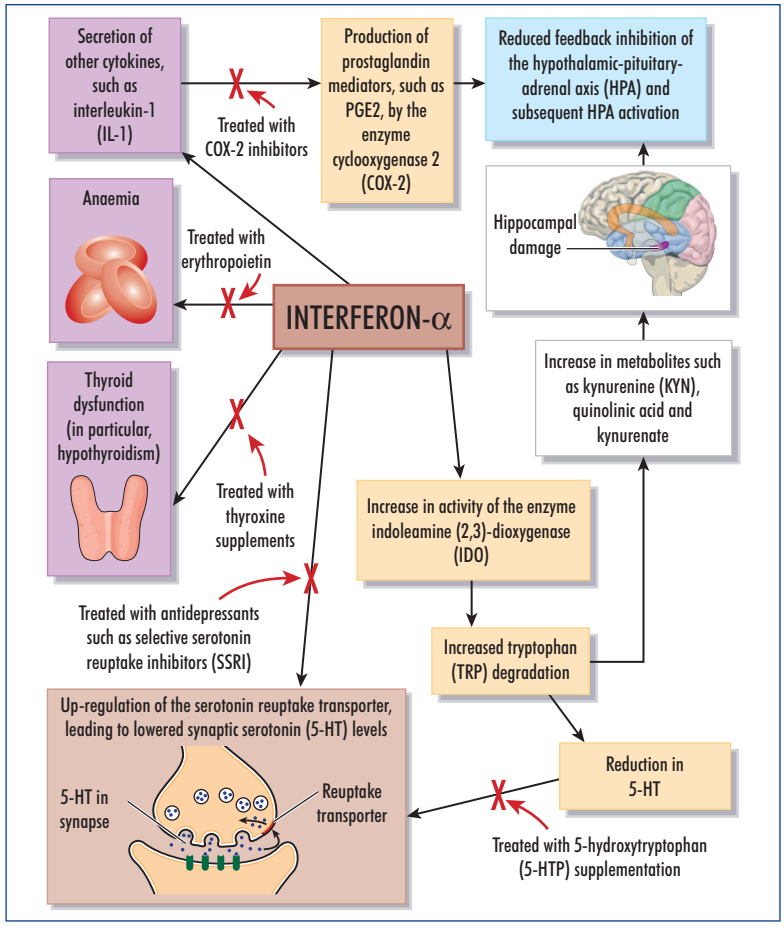
Finally, treatments that oppose accelerated tryptophan catabolism would include the use of IDO inhibitors. Although the IDO inhibitor 1-methyl TRP has been used in mice, it may not be without serious side effects in humans. It has been suggested that to treat IFN-induced depression adequately, 5-HT reuptake needs to be inhibited with an SSRI and in addition, 5-HT synthesis needs to be increased via supplementation with 5-HTP (Turner and Blackwell, 2005).

Figure 1 summarizes the possible mechanisms by which INF-α can lead to depression and where potential treatments may act.

Conclusions

Depression is a common side effect of IFN-α therapy. IFN-α may have direct actions on 5-HT and serotonin reuptake transporter, and may also act indirectly to reduce 5-HT and increase kynurenine metabolites via activation of the enzyme IDO. Kynurenine metabolites in turn may act upon reactive oxygen species or hippocampal NMDA receptors to promote apoptosis and suppress neurogenesis (Schiepers et al, 2005). Some antidepressants may act as effective prophylactic agents in patients with risk factors. Studies with SSRI and 5-HTP combinations may prove to be fruitful. In the

Figure 1. Mechanisms by which interferon-α can lead to depression and where potential treatments may act. Peripherally, interferon-α can lead to an anaemia that can be treated with erythropoietin. It can also lead to thyroid dysfunction, in particular hypothyroidism which can be treated with thyroxine supplements. There is also evidence for up-regulation of the serotonin reuptake transporter which can lead to lowered synaptic serotonin levels. This can be rectified with 5-hydroxytryptophan supplementation and treatment with antidepressants such as the selective serotonin-reuptake inhibitors. In addition, interferon-α can increase the activity of the enzyme indoleamine (2,3)-dioxygenase leading to increased tryptophan degradation with additional and consequent reductions in serotonin as well as increases in metabolites such as kynurenine, quinolinic acid and kynurenate. These metabolites have been shown to be neurotoxic to the hippocampus. This in turn can lead to reduced feedback inhibition of the hypothalamic–pituitary–adrenal axis and subsequent hypothalamic–pituitary–adrenal activation. Interferon-α can also lead to secretion of other cytokines, such as interleukin-1, that can also activate the hypothalamic–pituitary–adrenal axis via the production of prostaglandin mediators such as prostaglandin E2 (PGE2), by the enzyme cyclooxygenase 2. This hypothalamic–pituitary–adrenal activation can thus be inhibited by cyclooxygenase 2 inhibitors.



KEY POINTS

- Interferon-alpha therapy is significantly associated with depression.
- Risk factors include female gender, older age, higher depressive scores at baseline and a family history of depression.
- Interferon-alpha can activate the enzyme indoleamine (2,3)-dioxygenase. This can lead to reduced serotonin levels and increased toxic kynurenine metabolites.
- Antidepressants may be effective especially as prophylactic agents.

future there may be a role for pro-inflammatory cytokine receptor antagonists and drugs that modulate the prostaglandin system. **BJHM**

Conflict of interest: Dr Hafizi has no conflict of interest. Dr Favaron has previously been employed as a research psychiatrist by GlaxoSmithKline (Italy).

Angelino AF, Treisman GJ (2005) Evidence-informed assessment and treatment of depression in HCV and interferon-treated patients. *Int Rev Psychiatry* **17:** 471–6

Asnis GM, De La Garza R, 2nd (2005) Interferon-induced depression: strategies in treatment. *Prog Neuropsychopharmacol Biol Psychiatry* **29:** 808–18

Bonaccorso S, Puzella A, Marino V et al (2001) Immunotherapy with interferon-alpha in patients affected by chronic hepatitis C induces an intercorrelated stimulation of the cytokine network and an increase in depressive and anxiety symptoms. *Psychiatry Res* **105:** 45–55

Bonaccorso S, Marino V, Puzella A et al (2002) Increased depressive ratings in patients with hepatitis C receiving interferon-alpha-based immunotherapy are related to interferon-alpha-induced changes in the serotonergic system. *J Clin Psychopharmacol* **22:** 86–90

Cai W, Khaoustov VI, Xie Q, Pan T, Le W, Yoffe B (2005) Interferon-alpha-induced modulation of glucocorticoid and serotonin receptors as a mechanism of depression. *J Hepatol* **42:** 880–7

Capuron L, Dantzer R (2003) Cytokines and depression: the need for a new paradigm. *Brain Behav Immun* **17**(Suppl 1): S119–124

Capuron L, Miller AH (2004) Cytokines and psychopathology: lessons from interferon-alpha. *Biol Psychiatry* **56:** 819–24

Capuron L, Hauser P, Hinze-Selch D, Miller AH, Neveu PJ (2002) Treatment of cytokine-induced depression. *Brain Behav Immun* **16:** 575–80

Capuron L, Raison CL, Musselman DL, Lawson DH, Nemeroff CB, Miller AH (2003) Association of exaggerated HPA axis response to the initial injection of interferon-alpha with development of depression during interferon-alpha therapy. *Am J Psychiatry* **160:** 1342–5

Collantes-Estevez E, Fernandez-Perez C (2003) Improved control of osteoarthritis pain and self-reported health status in non-responders to celecoxib switched to rofecoxib: results of PAVIA, an open-label post-marketing survey in Spain. *Curr Med Res Opin* **19:** 402–10

Frick B, Capuron L, Schrocksnadel K et al (2004) Plasma homocysteine and immune activation in patients with malignant melanoma undergoing treatment with IFN-alpha. *J Interferon Cytokine Res* **24:** 311–17

Linthorst AC, Flachskamm C, Muller-Preuss P, Holsboer F, Reul JM (1995) Effect of bacterial endotoxin and interleukin-1 beta on hippocampal serotonergic neurotransmission, behavioral activity, and free corticosterone levels: an in vivo microdialysis study. *J Neurosci* **15:** 2920–34

Mann JJ (2005) The medical management of depression. *N Engl J Med* **353:** 1819–34

Meyers CA, Scheibel RS, Forman AD (1991) Persistent neurotoxicity of systemically administered interferon-alpha. *Neurology* **41:** 672–6

Musselman DL, Lawson DH, Gumnick JF et al (2001) Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N Engl J Med* **344:** 961–6

Raison CL, Capuron L, Miller AH (2006) Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol* **27:** 24–31

Saito K, Crowley JS, Markey SP, Heyes MP (1993) A mechanism for increased quinolinic acid formation following acute systemic immune stimulation. *J Biol Chem* **268:** 15496–503

Schiepers OJ, Wichers MC, Maes M (2005) Cytokines and major depression. *Prog Neuropsychopharmacol Biol Psychiatry* **29:** 201–17

Takikawa O (2005) Biochemical and medical aspects of the indoleamine 2,3-dioxygenase-initiated L-tryptophan metabolism. *Biochem Biophys Res Commun* **338:** 12–19

Turner EH, Blackwell AD (2005) 5-Hydroxytryptophan plus SSRIs for interferon-induced depression: synergistic mechanisms for normalizing synaptic serotonin. *Med Hypotheses* **65:** 138–44