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REVIEW ARTICLE

Interferon-Related Depression: A Primer on Mechanisms, Treatment, and Prevention of a Common Clinical Problem

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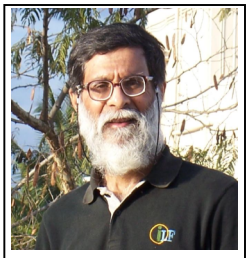
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Abstract: ***Background***: Depression is among the commonest of psychiatric disorders, and inflammatory mechanisms have been suggested to play a role in its pathophysiology. Interferons are a superfamily of proinflammatory cytokines that play a role in host defence mechanisms. Interferons are used in the treatment of a variety of autoimmune (*e.g.* multiple sclerosis), viral (*e.g.* chronic hepatitis B and C), and malignant (*e.g.* malignant melanoma, hairy cell leukemia) disorders; depression, however, is a notable and clinically troublesome adverse effect.

Objective: This article seeks to present a simple explanation and update for the reader about what interferons are, how interferons are classified, the clinical conditions in which interferons are used, the occurrence of depression as a clinical adverse effect of interferon therapy, possible mechanisms that explain interferon-related depression, the treatment of interferon-related depression, and the prevention of interferon-related depression.

Methods: A qualitative literature review is presented.

Results and Conclusions: Irrespective of the indication for IFN therapy, IFNs are associated with a 30-70% risk of treatment-emergent depression. This risk could be due to the IFN, or to an interaction between the IFN and the indication for which it was prescribed. Various neurohormonal, neurochemical, neurohistological, and other mechanisms have been put forth to explain IFN-related depression. Prophylactic treatment with antidepressants reduces the risk of IFN-related depression; antidepressants also effectively treat the condition. Recent alternatives to IFNs have shown to decrease the risk of treatment-emergent depression.

Keywords: Adverse effect, classification, depression, interferon, mechanism, prevention.

1. INTRODUCTION

Depression is among the commonest of psychiatric disorders, and inflammatory mechanisms are among the very many mechanisms that have been suggested to drive its pathophysiology [1]. Interferon-related depression is important in medicine and neurology, and the last decade has seen a spurt of research in the field. This article therefore summarizes the present state of knowledge about interferons and their role in depression in humans.

1.1. Interferons: General Introduction

Interferon (IFN) activity was first discovered by Isaacs and Lindenmann in the year 1957, when they came across a substance that interfered with the pathogenic activity of live influenza viruses in the chorioallantoic membranes of chick embryos that had previously been infected by heat-attenuated influenza viruses [2]. IFNs are a superfamily of cytokines that are endogenous and pleotropic in nature. They play a major role in host defence mechanisms and in maintaining homeostasis [3]. IFNs were the first cytokines to be discovered and the recombinant form of IFN-α was the first cytokine to be approved, in 1986, to treat hairy cell leukaemia [4, 5]. IFN species are distinctively different from one another in their functional profile; for example, they may exhibit antiviral and antiproliferative actvity, or they may stimulate antigen presenting cells [4]. This variation in activity is species-specific, and in a given species the IFN secretion is specific to the cell of origin and the virus eliciting the response.

1.2. Interferons: Classification

IFNs are classified as types I, II, and III (Table **1**), based on the cell surface receptors to which they bind [6]. The IFN type-I family consists of the following: 13 different IFN-α proteins coded by 14 IFN-α genes [4]; IFN-β, which is a product of the IFNB1 gene; and 6 other single gene-coded IFNs (IFN-ε, IFN-τ, IFN-κ, IFN-ω, IFN-δ, and IFN-ζ) [7, 8]. Type I IFNs can be produced by almost all cells in the body but are predominantly secreted by leukocytes (IFN-α) and fibroblasts (IFN-β) [7-9].

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Table 1. Classification of human interferons.

Type-I	IFN- α	IFNα1, IFNα2, IFNα4, IFNα5, IFNα6, IFNα7, IFNα8, IFNα10, IFNα13, IFNα14, IFNα16, IFNα17, IFNα21
	IFN-β, IFN-ε, IFN-τ, IFN-κ, IFN-ω, IFN-δ, and IFN-ζ	
Type-II	IFN-γ	
Type-III	IFN-λ1, IFN-λ2, IFN-λ3, IFN-λ4	

Table 2. Indications for interferon therapy.

Interferons	FDA Approved Indications for Interferon Therapy	Other Indications for Interferon Therapy
IFN- α	Chronic myelogenous leukemia, hairy cell leukemia, malignant melanoma, follicular lymphoma, condylomata acuminata, AIDS-related Kaposi's sarcoma, chronic hepatitis C, chronic hepatitis B	Recurrent respiratory papillomatosis, genital warts, Behçet's disease, chronic uveitic macular edema, bladder carcinoma, malignant carcinoid tumor, carcinoid syndrome, cervical cancer,malignant islet cell tumors, multiple myeloma, mycosis fungoides, non-Hodgkin's lymphoma (other than follicular lymphoma), thrombocytopenia, polycythemia vera, renal cell cancer
IFN-β	Multiple sclerosis	
IFN-γ	Chronic granulomatous disease, malignant osteopetrosis	

The type II IFN family consists of IFN-γ, coded by the IFNG gene that is predominantly secreted by T cells and natural killer (NK) cells. IFN-λ1, IFN-λ2 and IFN-λ3 (also known as IL-29, IL-28A and IL-28B, respectively) and IFN-λ4 (also known as IFNAN) form the IFN type-III family of cytokines that are secreted by all nucleated cells in the body. Other IFNs have been described in animals, but are not described here because they are out of the scope of the present article. Induction of types I and III IFNs (IFN-α, IFN-β, and IFN-ω; IL-28A, IL-28B, and IL-29) occurs after viral infection whereas type II (IFN-γ) is produced after stimulation with specific antigens such as staphylococcal enterotoxin A or B [4, 9].

1.3. Interferons: Signalling

Receptors for IFN family types I and II are present on all cells in the body and receptors for IFN family type-III are largely expressed on epithelial cells of the gastrointestinal and reproductive tracts, and on some immune cells [7, 8, 10]. The effector molecules involved in IFN downstream signalling that eventually results in their biological activity have not been completely defined in most cases, but one pathway that is strongly associated with IFN signalling is the JAK-STAT pathway [4]. In Type-I and III IFNs, the activation of JAK-STAT leads to the formation of IFN-stimulated gene factor-3 (ISGF3) complex which translocates to the nucleus and binds to the promoter region of IFN stimulated genes to bring about their transcription [4, 8, 10, 11]. Type-I and type-II IFNs also follow another pathway resulting in the transcription of IFN stimulating genes (ISG) by nuclear translocation and binding of STAT1-STAT1 homodimer to GAS (IFN-γ-activated site) elements on the promoter region of ISGs [11].

2. CLINICAL INDICATIONS FOR USE OF INTERFERONS

IFNs are used for the treatment of viral hepatitis, hemato-proliferative disorders, and autoimmune disorders and malignancies because of their antiviral, antiproliferative, and immunomodulatory properties, respectively. The immunogenic property of IFN-α has lead to the generation of IFN-α conditioned dendritic cells to induce tumor cell death, and also to its use as an adjuvant to enhance the antitumor effect of other chemotherapeutic agents [12].

Table **2** lists the USA Food and Drug Administration approved indications and other indications for interferon therapy [13-22].

Pegylation of the IFN molecule increases the size of the molecule and thereby increases the time that the molecule persists in the body [23]. Pegylated IFN-α, combined with ribavarin and protease inhibitors (optional), is the most common choice of treatment for hepatitis C infection [24]. Pegylated IFN-α is administered along with nucleotide analogues such as lamivudine, adefovir, entecavir, or tenofovir for chronic hepatitis B infections [25].

3. MECHANISMS FOR THE CLINICAL EFFICACY OF INTERFERONS

Many mechanisms are suggested to mediate IFN-related benefits; because this is a considerably speculative area, only a few, brief examples are provided. IFN-β may treat multiple sclerosis by inhibiting proinflammatory cytokines such as IL-17 and osteopontin; by increasing anti-inflammatory agents such as IL-10; by attenuating leukocyte migration across the blood-brain barrier; and by mediating tissue repair through stimulation of the release of trophic factors such as nerve growth factor [25]. In chronic granulomatous disease, IFN-γ is suggested to convey benefits by stimulation of the release of superoxide and correction of impairments in oxidative metabolism. Progression of malignant osteopetrosis is arrested by IFN-γ therapy putatively by improving osteoclast-mediated bone resorption and leucocytic superoxide production [25-27].

4. NEUROPSYCHIATRIC ADVERSE EFFECTS OF INTERFERONS

The neuropsychiatric adverse effects of IFNs include depression, irritability, anxiety, agitation, loss of appetite, fatigue, sleep disturbance, and impaired cognition; quality of life and functional abilities are consequently compromised. Importantly, attributing all these changes exclusively to IFN treatment can be difficult because the conditions for which IFNs are prescribed are often themselves associated with neuropsychiatric symptoms [28-30].

5. DEPRESSION AS AN ADVERSE EFFECT OF IFN THERAPY

Depression as a syndrome frequently complicates IFN therapy; the prevalence is 30-70% [29]. Depressive symptoms are common in the early stages of treatment, but typically peak between 4 and 16 weeks [31]. It is not always clear to what extent the risk is due to the IFN (and specifically to the type of IFN; *e.g.* IFN-α *vs.* IFN-β) and to what extent the risk is due to the clinical condition for which the IFN was prescribed. Therefore, risks are described separately in a later section. Here, we note that, for example, a meta-analysis of randomized controlled trials (RCTs) of IFNs in multiple sclerosis found no increase in the risk of depression as an adverse outcome [32]. Other meta-analyses, for example Coppola *et al*. [33] and Zhuang *et al.* [34] could not or did not provide data on depression outcomes. Conclusions from individual RCTs are hard to draw because these RCTs would not have been adequately powered to study depression as an outcome.

6. RISK FACTORS FOR INTERFERON-RELATED DEPRESSION

Patients with a past history of major depression are at increased risk of IFN-α related depression. The experience of certain depressive symptoms appears to predict an increased risk of depression as a syndrome; these symptoms include psychomotor retardation, somatic symptoms, and insomnia. Biochemical and other changes have also been associated with IFN-α related depression; examples include antiviral treatment-induced abnormal increase in the levels of interleukin-6, interleukin-10 and soluble interleukin-2 receptor (sIL-2R), and exaggerated response of the hypothalamo-pituitary adrenal axis after the first IFN dose. Possible genetic risk factors have been identified; examples include polymorphism in the transcription initiation site of the serotonin reuptake transporter gene (5-HT Transporter Linked Polymorphic Region [5-HTTLPR])- presence of short allele (s); C-1019G polymorphism of the transcriptional control region of the 5-HT1a receptor gene; AG polymorphism of the cyclo-oxygenase 2 (COX2) gene (rs4648308); GG polymorphism of the phospholipase A2 (PLA2) gene (rs10798052); CC genotype of interferon alpha/beta receptor 1 (IFNAR1). Higher dose and longer duration of IFN treatment are also associated with a higher risk of IFN-related depression. Finally, interferon treatment may interact with viral genotype, as in an increased risk of depression associated with hepatitis C viral genotype A [24, 28, 35-38].

IFN-β treatment-related depression in multiple sclerosis (MS) is not completely attributable to interferon therapy as the prevalence of depressive and suicidal symptoms in patients with MS is high in comparison with the general population. IFN-β therapy exacerbates depression in MS patients with a history of depression [39-42]. Pegylated IFN-β-1a is possibly less associated with depression and suicidal ideation [43].

There does not appear to be significant literature on the association between IFN-γ treatment and depression as a treatment-emergent adverse effect. The reason is unclear.

7. MECHANISMS THAT MAY UNDERLIE INTERFERON-RELATED DEPRESSION

Many mechanisms are suggested to underlie IFN-related depression. These are largely derived from animal models, are substantially speculative in nature, and are briefly outlined below.

The interaction between immune, endocrine, and neuronal pathways is believed to play an important role in interferon-related depression**.** IFN therapy (α, β) induces hypothalamo-pituitary-adrenal axis hyperactivity to release corticotropin releasing hormone (CRH) from the median eminence of the pituitary gland. CRH increases adrenocorticotropic hormone and hence adrenal corticosterone release. CRH also decreases serotonin and noradrenaline in the paraventricular nucleus, prefrontal cortex, hippocampus, and the central amygdala. These neuroendocrine and neurotransmitter changes are conventionally associated with risk of depression [28, 44].

IFN-α is suggested to modulate mood, behaviour, and the sleep-wake cycle by the activation of the proinflammatory cytokine network that comprises IFN-induced 15 kDa protein, ubiquitin-specific proteinase 18, guanylate binding protein 3, interleukin 1 (IL1), interleukin 6 (IL6), and tumor necrosis factor α (TNF-α), caspase-4, and caspase-8 or death-activating protein kinases [28, 44]. The possible role of proinflammatory cytokines in depression has recently been reviewed by Furtado and Katzman [45].

IFN-α treatment-mediated induction of c-jun N-terminal kinases (JNK), and p38 promote the expression of the beta

isoform of the glucocorticoid receptor, which is an inactive form of the receptor to which glucocorticoid binding does not result in the inhibition of proinflammatory cytokine release and inhibition of CRH release. These changes magnify the stress response and hence the risk of treatment-emergent depression [46].

μ opioid receptor activation by IFN-α and IFB-β increases brain prostaglandin E2 levels, in turn increasing indolamine 2,3-dioxygenase (IDO). IDO increases kynureninase, which inhibits kynurenine aminotransferase, resulting in excitotoxicity due to an imbalance between the NMDA receptor agonists (quinolinic acid and 3-hydroxykynurenine) and antagonist (kynurenic acid). This neurotoxic challenge causes a reduction in the density of serotonergic and adrenergic neuron, and loss of neurons in the hippocampus. These neurochemical and neurohistological changes predispose to depression [28, 44, 47-49].

In the adult mammalian brain, the dentate gyrus and the ventricular-subventricular zone on the lateral wall of the lateral ventricles harbor neural stem cells (NSC). These NSCs differentiate into neurons and neuroglial cells, and interference with this and related aspects of neuroplasticity is believed to predispose to depression [50]. Some of the mechanisms described earlier, such as release of corticosteroid hormones, dampen neuroplasticity in key structures such as the hippocampus and prefrontal cortex [50]. Additionally, proinflammatory cytokines such as IFN-α inhibit neurogenesis by inhibiting neural stem cell differentiation [51, 52].

Zheng *et al.* [53] found that IFN-α administration upregulates endogenous IFN-α production by activation of microglial cells, leading to inhibition of hippocampal neurogenesis. Administration of minocycline, an inhibitor of microglial activation, reversed CNS depression by reversing the effect of IFN-α on hippocampal neurogenesis.

8. TREATMENT OF INTERFERON-RELATED DEPRESSION

Currently, selective serotonin reuptake inhibitor (SSRI) drugs such as citalopram and paroxetine are administered to treat depressive symptoms that arise after IFN therapy [54, 55]. Paroxetine treatment has been found to attenuate anxiety symptoms, depressive symptoms, and cognitive dysfunction, but other symptoms, such as fatigue, psychomotor retardation, insomnia and anorexia do not respond [56]. In contrast, some data suggest that bupropion and modafinil may successfully treat neurovegetative symptoms such as insomnia, loss of appetite, and fatigue in the absence of mood and cognitive symptoms [28, 57].

IFN-α induced alteration in levels of monoamines in the brain, in areas such as the prefrontal cortex and hippocampus, may be attenuated by nonsteroidal anti-inflammatory drugs (NSAIDs). These drugs are commonly used to treat flu-like symptoms associated with IFN-α therapy and, as an additional benefit, are also known to augment the sustained virological response rate to IFN-α therapy in hepatitis C infection [13, 28]. The inflammatory hypothesis of depression notwithstanding, there are no suitable RCT data on NSAIDs in the treatment of the primary symptoms of depression as an IFN-related treatment-emergent adverse effect. The only study relevant to the subject [58] examined indomethacin augmentation (75 mg/day) vs no augmentation in metastatic malignant melanoma patients treatment with IFN- α2b. This study was small (47 evaluable patients) and hence underpowered for examining depression outcomes, short (most patients were treated for, apparently, 8 weeks, and so depression may not have had an adequate chance to develop), without a placebo control, did not describe how depression was diagnosed and evaluated, and actually found that confusion and depression was (nonsignificantly) more common in the indomethacin arm. Given the well-established efficacy of SSRIs in this regard, it is hard to expect that NSAID RCTs will be conducted in interferon-associated depression.

IFN therapy decreases tetrahydrobiopterin (BH4), a cofactor required for the biosynthesis of serotonin, dopamine, epinephrine, and norepinephrine, thereby predisposing to depression. BH4 levels can be increased by blocking reactive oxygen species and reactive nitrogen species production, or by the administration of folic acid, L-methylfolate, or S-adenosyl methionine [30]. These supplements have demonstrated varying degrees of success in the monotherapy or augmentation therapy of major depressive disorder, but treatment of IFN-related depression with these supplements has not so far been examined in randomized controlled trials and should therefore be considered as a possibility in the future.

9. EARLY DETECTION AND PREVENTION

Treatment-related depression and fatigue are the main causes of decreased treatment adherence to IFN regimes. Measures to improve and prevent depression begin with providing the patient with support to cope with the chronic illness and the stigma attached to it, bringing about lifestyle changes, and equipping the patient with information about the adverse effects of IFN therapy. It is important to monitor the patient during the initial phase of IFN therapy for early detection of significant changes in mood (however small) in order to reduce their progression; both psychosocial and pharmacological interventions may be implemented [29].

Udina *et al.* [60] conducted a systematic review and meta analysis to evaluate the safety and efficacy of SSRIs in preventing depression induced by IFN-α therapy in chronic hepatitis C patients**.** They identified 7 relevant randomized controlled trials (RCTs) and found that the prophylactic use of SSRIs reduced the odds of depression by 47%, relative to placebo. One RCT found that prophylactic treatment with omega-3 polyunsaturated fatty acids reduced the risk of treatment-emergent depression in hepatitis C patients receiving IFN therapy [59].

Research on hepatitis C virus replication has led to the discovery of newer, directly acting antiviral agents that target viral proteases and polymerases. Addition of these new antiviral drugs to an existing antiviral regimen (telaprevir, semiprevir, faldaprevir and boceprevir) or replacing the existing antiviral regimens with only direct-acting antiviral agents (ledipasvir/sofosbuvir regimen and the ombitasvir /paritaprevir/ritonavir and dasabuvir regimen) has shown

greater efficacy by sustained viral clearance, and as the required duration of antiviral therapy is reduced the duration of depression is also reduced [29, 61, 62]. In other words, using alternatives to IFNs would also reduce the risk of treatment-emergent depression in patients for whom such alternatives exist.

10. CONCLUDING NOTES

IFN treatment, regardless of indication, is associated with a 30-70% risk of treatment-emergent depression; there is probably an interaction between IFN and the indication for which the IFN is prescribed in the mediation of this risk. Many neurohormonal, neurotransmitter, neurohistological, and other mechanisms have been suggested to underlie the risk. The risk of IFN-related depression is attenuated by prophylactic treatment with SSRI drugs. SSRI and other antidepressant drugs are effective in treating IFN-related depression. Recent alternatives to IFNs may attenuate IFN-related risks.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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