Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Pharmacology

Psychological side effects of immune therapies: symptoms and pathomechanism

David Kovacs[1,7], Peter Kovacs[1,2,7], Nora Eszlari[1,4], Xenia Gonda[1,3] and Gabriella Juhasz[1,4,5,6]

Immunotherapies revolutionised the treatment of several disorders but show specific side-effect profiles which frequently involve psychological symptoms. Long term interferon-alpha (IFN-alpha) therapy can cause wide-ranging psychiatric side-effects from fatigue, insomnia, anxiety to full-blown depression. This treatment-emergent depression shares several symptoms with major depressive disorder (MDD) with a predominance of somatic/neurovegetative symptoms, and can be treated with antidepressants. However, this experience directed research to inflammatory mechanisms in MDD. MDD has been confirmed as a heterogeneous disorder with a subgroup of patients suffering from low-grade chronic inflammation and frequently resistant to traditional antidepressant treatment. Thus future research should develop strategies to identify those MDD patients who could benefit from drugs acting through inflammatory pathways.

Addresses
[1] MTA-SE Neuropsychopharmacology and Neurochemistry Research Group, Hungarian Academy of Sciences, Budapest, Hungary
[2] National Institute of Oncology, Budapest, Hungary
[3] Department of Clinical and Theoretical Mental Health, Kútvölgyi Clinical Center, Semmelweis University, Kútvölgyi u.4, Budapest, Hungary
[4] Department of Pharmacodynamics, Semmelweis University, Budapest, Hungary
[5] Neuroscience and Psychiatry Unit, University Manchester, Manchester, UK
[6] MTA-SE-NAP B Genetic Brain Imaging Migraine Research Group, Hungarian Academy of Sciences, Semmelweis University, Budapest, Hungary

Corresponding author: Juhasz, Gabriella (Gabriella.Juhasz@manchester.ac.uk)
[7] Equally contributed.

Current Opinion in Pharmacology 2016, **29**:97–103

This review comes from a themed issue on **Immunomodulation**

Edited by **Fulvio D'Acquisto**

For a complete overview see the Issue and the Editorial

Available online 22nd July 2016

http://dx.doi.org/10.1016/j.coph.2016.06.008

Introduction

Immunotherapy is a special biological therapy targeted at activating the innate immune system to fight infections or cancer, or downregulate immune response in case of autoimmune disorders or allergies. Immunotherapies that boost immune response against tumour cells or viruses are frequently associated with early neurovegetative symptoms characterised by fatigue, psychomotor slowing, anorexia and pain [1]. These symptoms show a significant overlap with the manifestations of the so-called sickness behaviour, caused by the activation of proinflammatory cytokines during infections and including symptoms of fatigue, anhedonia, low mood, social isolation and irritability [2]. Sickness behaviour is considered an adaptive response to promote healing by reducing energy expenditure towards not necessary activities and decreasing exploratory behaviour, thus it resembles a behavioural pattern very similar to anxiety and depressive symptoms. Depressive components including anhedonia, heightened pain sensitivity, and social avoidance are meant to conserve energy to fight the infection, while the anxious components were developed to avoid further conflicts which might have negative outcome on the healing process [3,4••]. Thus, an evolutionary advantageous behavioural effect of immune response, which enhances survival, is also a disturbing side effect of life saving immunotherapies leading to significant suffering, burden and loss of quality of life, and thus limiting the completion of the treatment course. Because of the sharp increase in the number of different immunotherapies and their indications in the present review we focus on the psychological side effects of the most frequently investigated interferon-alpha (IFN-alpha) treatment and shortly summarise the side effects of the newly developed immune checkpoint blocking agents.

Proinflammatory cytokines in the therapy: IFN-alpha

Interferons are a superfamily of proinflammatory cytokines that play a role in host defence mechanisms. IFN-alpha is a natural cytokine which has a synthetic version: IFN alpha-2b. IFN-alpha and IFN alpha-2b bind to interferon type-1 receptors, activating a signal transduction pathway leading to the expression of multiple genes responsible for inhibition of tumour cell growth and proliferation [5]. IFN-alpha is widely used in antiviral, for example, hepatitis C [6], and antitumor therapies such as malignant melanoma or hairy cell leukaemia [7,8].

Psychological symptoms during IFN-alpha therapy

Besides early neurovegetative symptoms which manifest in the majority of patients during the first weeks of IFN-alpha treatment as fatigue, pain and anorexia, long-term

IFN-alpha treatment often causes a wide variety of psychiatric side-effects, such as depression, fatigue, insomnia, anxiety, and cognitive disturbances [1]. 10–40% of patients additionally develop a full depressive disorder syndrome that can include suicidal ideation, aboulia, lack of motivation, social withdrawal, guilt, anhedonia, irritability, anxiety, and crying [9]. Mania, delirium, and psychosis are further but less common side effects of IFN-alpha treatment. Approximately 30–70% of hepatitis C virus-infected patients treated with IFN-alpha experience different degrees of depression. Most of them suffer from mild or moderate depressive symptoms, while severe major depression occurs in about 15% [10].

In addition to these similarities, the symptom profile (Table 1) of treatment-emergent depression and naturally occurring major depressive episode show some distinctions [11]. Namely, during long-term IFN-alpha treatment patients reported more severe weight loss and decreased activity, while feeling of guilt was less prominent compared to medically healthy depressed subjects [12]. This observation was supported by a recent finding which suggested that risk genetic variant in the *IL-6* gene more specifically increased depressive symptoms measured by the Zung Self-rating Depression Scale compared to the Brief Symptom Inventory, suggesting that inflammatory risk mechanisms are more responsible for somatic/neurovegetative symptoms than cognitive-emotional signs of depression [13]. Furthermore, newly developed immune checkpoint inhibitors, such as anti-cytotoxic T-lymphocyte anti-gen 4 (CTLA-4) antibodies or humanised immunoglobulins against programmed death 1/ligand 1 (PD-1/PD-L1) which also enhance tumour-specific immune activity are associated with a new category of side effects called 'immune-related adverse events' (irAE), in which the most frequent symptom is fatigue [14]. However, treatment-induced depression has not been detected in relation to these new drugs [15].

Distressing and frequently untreated depression is a major contributor to dosage reductions or treatment discontinuations during IFN-alpha therapy and consequently increases the risk of ineffective treatment outcome or relapse [16,17]. Thus, it is of great clinical importance to investigate the mechanism underlying IFN-alpha-induced depression and possible preventive strategies.

Potential mechanisms of IFN-alpha-treatment-induced depressive symptoms

IFN-alpha is a strong activator of the proinflammatory cytokine system by increasing the peripheral concentration of interlekin-6 (IL-6), interleukin 1-beta (IL-1β) and tumour necrosis factor-alpha (TNF-α) [18]. Recent neuroimaging findings showed that acute administration of IFN-alpha elicited an instant and profound decrease in brain functional network connectivity which resulted in changes in mood and cognitive symptoms [19••]. In addition, long-term IFN-alpha treatment was associated with increased glutamate level in the basal ganglia and dorsal anterior cingulate cortex (dACC) [20] which might explain the previously reported increased ACC activation and impaired error processing in IFN-alpha treated patients [21].

However, remain the question how the cytokine imbalance in peripheral plasma samples, induced by IFN-alpha treatment, could spread into the brain which is protected

Table 1

Symptom profile of sickness behaviour, major depressive disorder, IFN-alpha induced depression, and psychological side effects of immune checkpoint inhibitors

Symptom domain	Symptom	Sickness behaviour	MDD	IFN-α	ICI
Mood	depressed mood	x	xxx	xxx	
	anhedonia	x	xxx	(x)	
	guilt		x	(x)	
	suicidal thoughts		x	(x)	
Anxiety	tension/irritability	x	x	xx	
	fear	x	x	xx	
Cognitive	memory/concentration		x	x	
	decision making		x	x	
Somatic/neurovegetative	appetite	x	x	xxx	
	sleep	xx	x	x	
	psychomotor retardation	xx	x	xxx	
	fatigue	xx	x	xxx	xxx
	pain	x	x	xxx	

MDD: major depressive disorder, IFN-alpha: interferon alpha treatment, ICI: immune checkpoint inhibitor treatment, x: symptom is present, number of x: dominance of symptoms

MDD: major depressive disorder, IFN-alpha: interferon alpha treatment, ICI: immune checkpoint inhibitor treatment, x: symptom is present, number of x: dominance of symptoms.