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Psychological side effects of immune therapies: symptoms and pathomechanism

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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.

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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

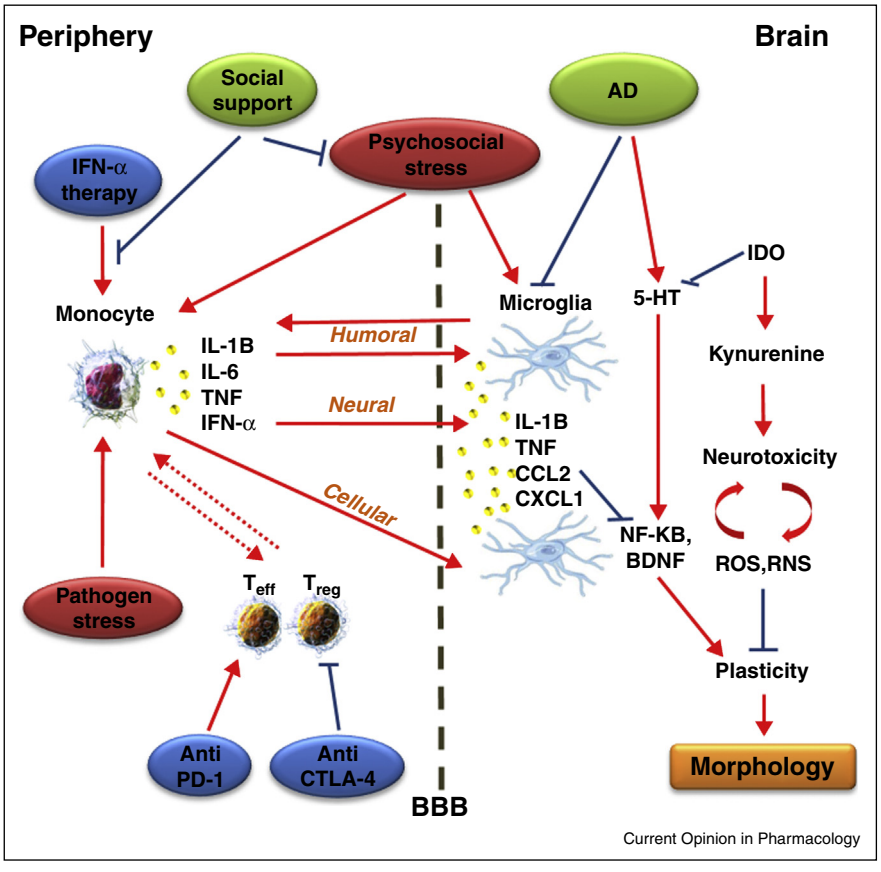
MDD: major depressive disorder, IFN-alpha: interferon alpha treatment, ICI: immune checkpoint inhibitor treatment, x: symptom is present, number of x: dominance of symptoms.

by the blood–brain barrier (BBB) (Figure 1). There are three main proposed pathways how inflammatory activation can reach the brain to exert its effect on mood. First, cytokine molecules can cross the BBB in some areas using specific transport proteins, and also by non-specific transport in the circumventricular organs, including the area postrema, or the subfornical organ. Second, afferent nerve fibres (e.g. vagus) can also carry the inflammatory signals to the brain when inflammatory cytokines bind to cytokine receptors and transmit these signals into the central nervous system [22]. Third, there is a cellular pathway where whole activated immune cells can reach the brain with the help of CC-chemokine ligand 2 (CCL2), and CXC-chemokine ligand 1 (CXCL1). Peripherial cytokines, such as TNF, can induce the transport by activating the microglial production of these chemokines, and also by inflammatory stimulated astrocytes [23]. Post mortem studies of suicide victims who also suffered from depression revealed increased CCL2 expression and macrophage numbers in the perivascular space, suggesting increased transport of activated immune cells into the brain in depressive state [24].

Decreased neural plasticity

Besides activated cells crossing the BBB, microglial cells which have the original purpose of fighting infections inside the CNS also produce cytokines such as TNF-α and IL-1β. Overactivation of microglial cells is commonly reported in association with depressive states. Prolonged elevation of cytokine levels inside the brain can induce

Figure 1



Potential role of immune mechanisms in immunotherapy-induced and stress-induced depression. Activation of the immune system during specific immunotherapies or by infections and sterile stressors like childhood maltreatment, recent negative life events or chronic pain induces depression-related mechanisms. The inflammatory signal of activated immune cells can cross the blood–brain barrier (BBB), and reach the central nervous system by various pathways. The main coordinators of this transport are the microglial cells, producing attracting chemokines, and facilitating the transport of activated immune cells through the blood–brain barrier. Microglial cells can also be activated by psychosocial stress. The proinflammatory signal in the brain works in the opposite direction compared to the effect of antidepressants, suppressing 5-HT activity, and activating the kynurenine pathway. The neurotoxic kynurenine metabolites, and the lower BDNF and NF-KB levels promote reduced neural plasticity, and also oxidative radicals damage neural pathways leading to depression-specific morphological changes. 5-HT: serotonin, AD: antidepressants, Anti CTLA-4: antibody against anti-cytotoxic T-lymphocyte anti-gen 4, Anti PD-1: antibody against programmed death 1/ligand 1, BDNF: brain derived neurotrophic factors, CCL2: CC-chemokine ligand 2, CXCL1: CXC-chemokine ligand 1, IDO: indolamine-2,3-dioxygenase, IL-1B: interleukin 1-beta, IL-6: interlekin-6, INF-α: interferon-alpha, NF-KB: nuclear factor κB, ROS: radical oxygen species, RNS: radical nitrogen species, T_{eff}: effector T lymphocytes, T_{reg}: regulatory T lymphocytes, TNF: tumour necrosis factor.

neural apoptotic pathways through their effect on nuclear factor κB (NF-κB) and brain-derived neurotrophic factor (BDNF), resulting in impaired neuronal plasticity, and promoting depression-specific morphological alterations [25].

Decreased neurotransmitter availability

Proinflammatory cytokines can also influence neural plasticity through the activation of indolamine-2,3-dioxygenase (IDO) which is the rate limiting enzyme of kynurenine production. IDO is an enzyme which converts tryptophan into kynurenine, thus competing for tryptophan with the serotonine pathway [26]. Lower tryptophan availability itself can cause depressive symptoms under experimental conditions, but lower serotonergic function is also commonly found in depressed individuals.

Increased neurotoxicity

Besides the lower amount of tryptophan left for serotonin synthesis, activation of the kynurenine pathway also produces potentially neurotoxic metabolites. For example, quinolinic acid which is elevated in post-mortem depressed suicide victims' brain acts as an N-methyl-D-aspartate (NMDA) receptor agonist, and also contributes to disturbances in glutamate reuptake and release from astrocytes, leading to excitotoxic neuronal damage [27]. Interesting to note that IDO hyperactivity correlated with long-term depression-specific symptoms (depressed mood, anxiety) but not with early neurovegetative symptoms (pain, fatigue, anorexia) during cytokine therapy [28].

Increased oxidative stress

Inflammatory activation is also accompanied by increased production of radical oxygen (ROS) and radical nitrogen species (RNS). The activity of tetrahydrobiopterin (BH4) which is necessary for monoamine synthesis, is reduced by oxidative radicals, suggesting lower synthesizing capacity in the presence of inflammation. These oxidative substances are damaging for DNA, fatty acids, and proteins alike especially in neural cells which are the most vulnerable to oxidative stress. Alterations in neural cell membrane structure, serotonin binding capability, and intracellular signalling mechanisms due to oxidative stress all contribute to impaired serotonergic activity and tissue damage. Furthermore, superoxide anion radicals (SAR) behave as a co-substrate of IDO causing superinduction of the kynurenine pathway in the presence of excessive oxidative stress, thus oxidative radicals and kynurenine seems to form a self-enhancing loop which reduces the survivability of neuronal cells greatly [29].

Difference between the mode of action of IFN-alpha and immune checkpoint inhibitors

Although both IFN-alpha and immune checkpoint inhibitors increase tumour specific immune response their psychological side-effect profiles are strikingly different. It has been recently demonstrated that CTLA-4 antibodies (e.g. ipilimumab) decrease the number of regulatory T_{reg} cells through non-classical monocytes [30]. Nonclassical or patrolling monocytes are responsible for clearing up the consequences of inflammation at the vascular endothelium and maintaining the integrity of the BBB thus they might decrease expansion of the inflammation into the central nervous system [31]. PD-1/PD-L1 antibodies (e.g. nivolumab and pembrolizumab, both approved in 2014) increase effector T cell activity within tissues or tumours where cells express PD-1/PD-L1 which tends to be low in the brain [14,32].

Risk factors of psychological side effects during IFN-alpha treatment

It has been observed that behavioural effect of inflammation shows differences between patients. Thus knowledge of risk factors for developing depression would be useful in clinical practice to prevent such adverse effects [33]. One major risk factor is presence of psychiatric disorders, especially depression in the medical history possibly because of shared biological mechanisms. For example, it has been demonstrated that increased prevalence of depression in females might be explained by the greater sensitivity of females to inflammatory signals both at the biochemical and behavioural level [34].

Potential genetic risk factors

Genetic variants that have been implicated in depression like the serotonin transporter gene functional promoter polymorphism (*5-HTTLPR*) [35,36], or other serotonin (e.g. *HTR1A*) or inflammatory (e.g. *IL-6*, *COX-2*, *TNF-alpha*) pathway related genetic variants increase the risk of developing psychological side effects during IFN-alpha treatment [33,37]. Furthermore, several genetic variants throughout the interferon α/β signalling pathway [38••], and genetic variants in the *IL-6*, *IL-1β* or nitric oxide synthase-1 (*NOS1*) genes increase depressive and anxiety symptomatology, especially in the presence of psychosocial stressors in general populations [13,39•,40].

Psychosocial stress

It has been consistently reported that psychosocial stress is a potent inductor of inflammatory response both in animals and humans [41,42]. Sterile stressors, like negative life events, are able to activate inflammosomes, a complex cytosolic protein cascade with the original role in pathogen host-defence reaction. The main products of inflammosomes are inflammatory cytokines such as IL-1B, Il-6, TNF-α, and CRP [22,43]. These cytokines are considered to be one of the most stable biomarkers for depression. In addition, stress exerts not only an acute but a long-term effect on inflammation. For example, childhood trauma permanently upregulates proinflammatory cytokines, probably through epigenetic changes [25,44]. In addition, patients with sensitized stress response pathways are more vulnerable to interferon IFN-alpha-induced depression. For example, patients who responded to a first dose of

IFN-alpha with hyperactivity of the hypothalamic-pituitary-adrenal axis (HPA) were significantly more likely to develop major depression during treatment than patients with modest stress system responses to the initial injection [45].

Social support as a protective factor

It is important to note that social support is able to decrease the risk of depression both in a general population and in patients treated with immunotherapies [46]. Social support has been associated with decreased HPA activity and glucocorticoid concentration [47,48], with diminished dACC activity after social stressor [48], and with decreased proinflammatory cytokine production during stress [49]. Indeed, melanoma patients with increased social support were less likely to develop depressive symptoms during low-dose IFN-alpha treatment [50•].

Prevention of IFN-alpha induced psychological symptoms

Screening and evaluation of risk factors such as psychiatric history, genetic polymorphisms, premorbid elevations in inflammatory cytokines, or social support may help to initiate personalized prevention therapy in those who are likely to develop psychiatric side effects during IFN-alpha treatment [9]. Multiple studies found that prophylactic and concurrent treatment with selective serotonin reuptake inhibitors (SSRIs) successfully reduced the incidence and severity of major depression in patients with chronic hepatitis C infection or malignant melanoma treated with IFN-alpha-2b [51•]. In addition, preliminary studies suggest that a diet rich in omega-3 polyunsaturated fatty acids which promote anti-inflammatory processes in the body and may also process mood-stabilising effects thus may prevent somatic depressive symptoms in cytokine-treated patients [52]. However, it is interesting to note that (non IFN-alpha induced) major depressive patients with an elevated inflammatory biomarker profile typically respond poor to standard antidepressant or antipsychotic treatment [53].

Conclusions of experience with immune-influencing agents for treating major depressive disorder

Introduction of immunotherapies have not only advanced the treatment of tumours, virus infections, autoimmune diseases and allergies but also shed light on the pathomechanism of depression. Now it is increasingly accepted that major depressive disorder is a heterogeneous condition concerning both its manifestation and its underpinnings, and covers several distinct ethiopathologic routes, one of them being chronic low grade-inflammation, that converge to the emergence of similar symptoms [4••]. Indeed, SSRI-type antidepressants are able to counteract the effect of inflammatory mechanisms of depression to a certain degree. For example there is experimental evidence that release of TNF-α, NO, and IL-6 from microglial cells in response to IFN-γ administration can be impaired by certain SSRI-type antidepressants [54], and they are able to shape the immune response in the peripheral immune cells as well [55•]. However, as mentioned above, an elevated inflammatory biomarker profile predicts poor treatment response to first choice (typically SSRI) antidepressants. For example, patients with higher C-reactive protein levels improved better on nortriptyline compared to escitalopram [56]. Thus, patients who are refractory to standard antidepressant pharmacotherapies should be screened for inflammatory biomarkers to adjust their treatment. Supporting the alternative therapeutic approach there are studies reporting cyclooxygenase and nitric oxide synthase inhibitors exerting antidepressant-like activity [29]. In addition, minocycline, an antibiotic substance with capability to reduce microglial activation was able to restore hippocampal neurogenesis and thus a potential candidate in depression treatment [57]. Moreover, TNF-α antagonist infliximab showed a higher reduction of depression scores compared to placebo in patients with treatment-resistant depression and higher CRP levels [58]. Thus drugs targeting the inflammatory biological pathways might be a way forward in a subset of depressed patients who do not improve on standard antidepressant treatment.

Conflict of interest

David Kovacs is an employee of Gedeon Richter Plc. Medical Division, but the company did not provide any funding, or had any further role in the preparation of the article. The other authors did not declare any conflicting interests.

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