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THE IMPLICATIONS OF THE NEUROTROPHIC FACTOR TNF-α IN DEPRESSIVE DISORDERS

Andreea Roșian[1], associate professor Mihaela Zdrîncă[2], full professor Luciana Dobjanschi[2], full professor Laura Grațiela Vicaș[3], researcher Iulius Liviu Mureșan[4], researcher Constantin Florian Negruț[5], full professor Mariana Eugenia Mureșan[2], full professor Eleonora Marian[1,3]
1 - Doctoral School of Biomedical Science, Faculty of Medicine and Pharmacy, University of Oradea, Oradea, Romania (A.R. – https://orcid.org/0009-0003-8382-6720, E.M. – https://orcid.org/000-0002-6181-1590)
2 - Department of Preclinical Discipline, Faculty of Medicine and Pharmacy, University of Oradea, Oradea, Romania (M.Z. – https://orcid.org/0000-0001-9487-0939, L.D. – https://orcid.org/000-0003-3768-1617, M.E.M. – https://orcid.org/000-0003-4403-6091)
3 - Department of Pharmacy, Faculty of Medicine and Pharmacy, University of Oradea, Oradea, Romania (L.G.V. - https://orcid.org/000-0001-5328-333X)
4 - CMI Dr. Iulius Liviu Mureșan, Oradea, Romania
5 - Spitalul Clinic Județean de Urgență Bihor, Oradea, Romania

INTRODUCTION

Major depressive disorder (MDD) is a devastating affective disorder, being the most prevalent psychiatric disorder. The prevalence of MDD globally, between the years 1990 and 2019, is presented in Figure 1. The World Health Organization (WHO) estimates that, by 2030, depression will have become the leading cause of disability worldwide.

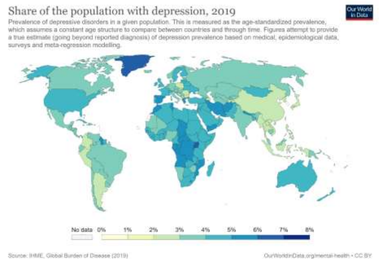

Figure 1. The prevalence of MDD globally, between the years 1990 and 2019.

In recent years, the efficacy of antidepressant medication compared to placebo has become increasingly difficult to demonstrate in clinical studies. It has been observed that only about half of the patients with depression achieve complete remission.

Research conducted in the recent period has brought to attention the fact that cytokine inflammatory system is activated in several disorders, including depressive states. It seems that tumour necrosis factor alpha (TNF-α) plays an important role in the pathophysiological mechanisms of the development of depressive syndrome, as it is involved in inflammation and programmed cellular apoptosis. We can state that TNF-α would intervene through two mechanisms. Firstly, it is assumed that TNF-α is involved in the regulation of a serotoninergic neuronal transporter that stimulates serotonin uptake. Secondly, it is believed that it can intervene in the activation of the enzyme indolamine 2,3-dioxygenase (IDO) that favours the degradation of tryptophan, reducing serotonin availability in depression states.

TNF-α is a multi-functional cytokine known for its major role in regulating inflammatory responses. Numerous studies have highlighted increased concentrations of TNF-α in patients with depressive episodes compared to control groups. All these make it necessary to discover biomarkers that will allow us to understand the pathogenesis of the disease, monitor the efficacy of the treatment and identify new therapeutic targets.

AIM AND OBJECTIVES

- The aim of the study involved reviewing the potential of TNF-α as a biomarker in depression and evaluating the capacity of TNF-α inhibitors in reducing depressive symptomatology.

MATERIALS AND METHODS

This is a study report that includes a selection of scientific evidence necessary for reviewing the potential of TNF-α as a biomarker in depression and evaluating the ability of TNF-α inhibitors in reducing depressive symptomatology.

DISCUSSIONS

MDD:

Mood disorders, also known as affective disorders, are characterized by external manifestation of mood, namely the emotion felt at the inner self, and include two extremes of the spectrum: mania and depression. MDD is a condition with a major impact on public health, a medical and socio-economic burden that affects the individual's ability to function and integrate themselves into society.

INVOLVEMENT OF THE INFLAMMATORY PROCESS IN DEPRESSION:

Numerous studies have shown a link between inflammation and depression, thus suggesting the involvement of additional mechanisms in the pathogenesis of MDD. It has been found that approximately 30% of patients with MDD have a disruption of the inflammatory process, with an increase in the concentration of inflammatory markers. Constantly elevated levels of inflammatory cytokines stimulate the hypothalamus-pituitary-adrenal axis (HPA) and increase the production of corticotropin-releasing hormone (CRH). Indirect consequences include the development of glucocorticoid resistance and modification of neurotransmitter concentration that are interpretated by the brain as stressors. In addition, the induction of serotonin transporter expression, which leads to decreased serotonin levels, and elevated activity of IDO, responsible for the production of a neurotoxic metabolite, are other mechanisms involved in the pathogenesis of depression.

Thus, increased chronic inflammation induced by altered cytokines concentration leads to cognitive decline, which may be responsible for the appearance of symptoms similar to those in depression.

Moreover, it has been highlighted that patients with conditions caused by modifications of the inflammatory process are at a much higher risk of depression.

However, the presence of inflammation is not specific to MDD, as concentrations of pro-inflammatory cytokines can also be increased in other conditions, both psychiatric and non-psychiatric.

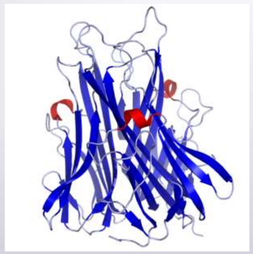

Figure 2. The structure of TNF-α.

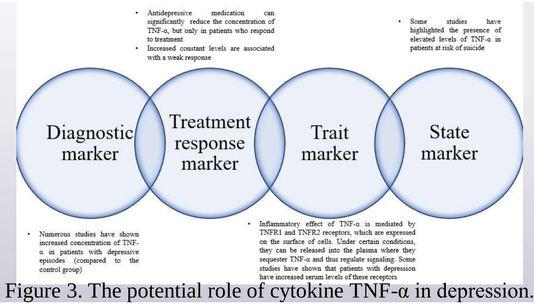

Figure 3. The potential role of cytokine TNF-α in depression.

TNF-α:

TNF-α is an inflammatory marker with an important role within biological processes, such as immunomodulation and the inflammatory response. Structurally, it is a homotrimer protein consisting of 157 amino acids (figure 2), being classified as a member of TNF transmembrane protein superfamily.

TNF-α is synthesized in the cell membrane, where it is proteolytically cleaved by an enzyme, resulting in its soluble form. Both the transmembrane and soluble forms are biologically active, and their mechanism of action involves binding to specific receptors (TNFR1 and TNFR2). TNF-α receptors produce similar effects, such as immune defence, induction of inflammation, promotion of cell proliferation and survival, as well as different effects. For example, TNFR1 is involved in processes such as inflammation, apoptosis and necrosis, while TNFR2 influences host defence, tissue repair and regeneration.

Numerous studies have shown the potential role of cytokine TNF-α as a diagnostic marker, treatment response marker, trait or state marker in MDD (figure 3).

DISCUSSIONS

TNF- α INHIBITORS:

The information obtained from specialized literature has highlighted the fact that elevated chronic inflammation leads to an increased concentration of inflammatory mediators, resulting in depressive symptoms, and that patients with conditions characterized by changes in inflammatory process are at a much higher risk of depression. Based on this evidence, the role that TNF-α inhibitors could play in reducing depressive symptomatology has been suggested.

In this regard, researchers have conducted numerous studies to investigate the effect of TNF-α inhibitors on depressive symptoms accompanying some inflammatory conditions (Table 1).

Infliximab has also been studied in patients with psychiatric conditions, with an improvement in symptoms observed for certain subgroups.

A randomized, double-blind, placebo-controlled study has demonstrated the efficacy of pentoxifylline in subjects with MDD (Table 2).

Table 1. The effect of TNF-α inhibitors on depressive symptoms accompanying some inflammatory disease

Inflamatory disease	TNF-α inhibitor	Effect
Crohn's disease	Infliximab Adalimumab	Significant decrease in depressive symptoms
Psoriasis	Etanercept Adalimumab	Significant decrease in depressive and anxiety symptoms
Ankylosing spondylitis	Infliximab	Significant decrease in depressive symptoms
Hidradenitis suppurativa	Adalimumab	Significant decrease in depressive symptoms in patiens with high baseline pain score

Table 2. The effects of infliximab in patients with psychiatric conditions and the efficacy of pentoxifylline in subjects with MDD

TNF-α inhibitor	Disease condition	Effect
Infliximab	MDD (treatment-resistant)	Significant decrease in depressive symptoms in a sub-group of patients with high baseline CRP levels
	Bipolar depression	Significant decrease in depressive symptoms Improvement in cognitive function
	Bipolar depression with higher inflammatory activity	Significant decrease in depressive symptoms in patients with a history of childhood physical abuse
Pentoxifylline	MDD	Significant decrease in depressive symptoms

CRP = C-reactive protein

CONCLUSIONS

- 1. MDD is a devastating affective disorder, a major cause of disability worldwide.
- 2. The increasingly difficult to demonstrate efficacy of antidepressant medication has made it necessary to discover new therapeutic targets.
- 3. The implication of TNF-α in the pathogenesis of MDD has allowed for studies to be conducted aimed at evaluating the ability of TNF-α inhibitors to reduce depressive symptomatology.
- 4. Further studies are needed to directly examine the modulating effect of TNF-α inhibitors in order to identify new therapeutic targets that could improve the therapeutic management of patients with MDD.

KEYWORDS

depression, TNF-α, inflammation, TNF-α inhibitors