Psoriasis: Treating the Skin and the Mind

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Abstract

Psoriasis is a debilitating autoimmune disease defined by erythematous, pruritic, and scaly plaques. Yet, this disease also has numerous extracutaneous associations including depression, heart disease, arthritis, and inflammatory bowel disease. The combination of physical and mental manifestations of psoriasis can be explained, respectively, by inflammatory cytokines that act on skin cells to create scaly patches and brain cells to alter one's mental state. In light of such discoveries, this paper discusses the novel use of psoriasis medications such as tumour necrosis factor-α blockers, anti-interleukin-1β antibodies, and anti-interleukin-6 antibodies to address mood and anxiety disorders.

Introduction

Named after the Greek word for "scaly," psoriasis is marked by raised, erythematous plaques covered with silvery paches.[1] It primarily affects flexural skin surfaces such as elbows and knees, but can also affect other parts of the body such as nails, joints, and the brain.[1] Moreover, this chronic disease affects overall quality of life, thus necessitating examination of both psychosocial and physical aspects of the disease for management.[2-5]

Numerous topical and systemic therapies are tailored towards the cutaneous manifestations of psoriasis, with treatment options depending on disease severity, individual patient response, and efficacy.[2] As an autoimmune skin condition, psoriasis is currently managed with topical steroids that dampen the inflammatory response. However, topical steroids are not selective for the disease-causing cells and thus produce various side-effects such as atrophy, striae, and hypopigmentation.[6] Furthermore, systemic therapy and phototherapy are available for moderate and severe cases of psoriasis, defined as involvement of more than 5-10% of the body surface area, or involvement of the face, palm, sole, or other body parts that are otherwise disabling.[2] However, these treatment options are costly, inconvenient, and prone to severe side-effects.[6] In fact, patient dissatisfaction is evident through the analysis of surveys performed by the National Psoriasis Foundation, showing that 52% of 5604 survey respondents with psoriasis expressed dissatisfaction with their treatment.[7]

Biologic agents used in the treatment of severe psoriasis include anti-tumour necrosis factor (TNF) agents as well as anti-interleukin (IL) antibodies.[2] It is possible to approach disease management by targeting inflammatory cells that are pathognomonic of psoriasis. In fact, immune modulators involved in the cutaneous pathogenesis of this disease also act on the central nervous system, contributing to increased rates of depression and anxiety in psoriasis patients.[1,8]

Understanding how cytokines distribute in the body provides further clues as to how they affect inflammation and depression. This process starts when stress signals induce the release of modulators such as corticotropin-releasing hormone (CRH) and substance P, which trigger mast cells to start the inflammatory process.[9] In turn, peripheral inflammatory cytokines such as TNF-α, IL-1β, and IL-6 induce microglial inflammation in the brain while promoting apoptosis via receptor binding in the skin.[10,11] Furthermore, stress signals also travel from the brain and spinal cord to the peripheral nervous system. Given the involvement of the central and peripheral nervous system in psoriasis, recent studies have investigated the cross-utilization of medications for psoriasis and mental disorders.[1,9] These studies include the use of TNF-α blockers and anti-IL antibodies for the treatment of psychoactive disorders such as major depressive disorder, bipolar disorder, and generalized anxiety disorder.

TNF-α Blockers for Anxiety, Depression, and Bipolar Disorder

With the understanding that inflammatory cytokines can lead to physical and emotional symptoms in psoriasis, there is work underway to develop new medications that can stop inflammation, stress, and depression altogether. At the same time, it is important to note that pre-existing treatments for each of these conditions can also be used to target this common route of pathogenesis. For instance, certain TNF-α inhibitors such as etanercept and infliximab that are currently used to treat psoriasis can also alleviate depression through serotonin disruption in the brain and activation of hypothalamo-pituitary-adrenocortical (HPA) axis.[12-14]

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Pro-inflammatory cytokines such as TNF-α influence affective disorders by up-regulating serotonin transporter (SERT) activity, activating the enzyme indolamine-2,3-dioxygenase (IDO) as well as the HPA axis.[10,14] Both SERT and IDO reduce serotonin availability, while HPA activation leads to the release of CRH, adrenocorticotropic hormone (ACTH), and cortisol.[14] In addition, IDO activation leads to serotonin depression by converting tryptophan in kynurenine, which is further converted to the N-methyl-D-aspartate receptor agonist, quinolinic acid. Quinolinic acid, in turn, induces lipid peroxidation and oxidative stress, thus leading to a self-propagating cycle of neurodegeneration involving IL-1β, TNF-α and IFN-γ cytokines.[15]

Studies have supported the anti-depressant effects of etanercept on patients with major depressive disorder (MDD) and bipolar disorder (BD).[12] In one study, depression was measured via the Hamilton Depression Rating Scale (HAMD-21) and self-rated Beck Depression Inventory (BDI-II). Following a wash-out period of 14 days, depressive symptoms were quantified after 7, 14, and 21 days of etanercept monotherapy. The results demonstrated that TNF-α blockers reduced the prevalence of both major depressive disorder and bipolar disorder, reducing HAMD-21 score by 25 points and BDI-II score by 13 points after merely 7 days.[12]

Anti-TNF-α therapy has also been used in 83 consecutive rheumatoid arthritis patients to alleviate mood and anxiety disorders.[13] In one study, psychiatric disorders were defined using the Structural Clinical Interview for DSM-IV.[13] Similar to psoriasis, rheumatoid arthritis is an inflammatory disorder associated with depressive (34.9% of patients) and anxiety disorders (22.9% of patients).[13] TNF-α antagonists like etanercept and inflixumab also reduced the prevalence of psychiatric conditions in rheumatoid arthritis patients.[13]

Anti-IL Antibodies for Anxiety and Depression

In addition to TNF-α, there are numerous ways in which inflammatory cytokines can alter brain activation and behaviour.[16] Cytokines like IL-6 and IL-1β can cross the blood-brain-barrier using saturable transport mechanisms and act directly on microglia, astrocytes, and neurons throughout the CNS. This further affects physiological processes such as neuronal differentiation and survival as well as astrocyte proliferation. Furthermore, microglia activation stimulates the surrounding glia to allow inflammatory monocytes to enter the affected brain regions. Once inside the brain, these monocytes differentiate into microglia and produce local inflammatory responses that contribute to anxiety. Furthermore, interleukins also modulate astrocyte receptors. Astrocytes typically line the blood-brain-barrier, thus preserving the integrity of the barrier and acting as a filtering agent. Increasing peripheral cytokines changes the transcriptome profile of astrocytes and further upregulates the cytokines that are released into the central nervous system.[16] Interestingly, chronic stress acts by decreasing astrocytic volume and branching pattern as opposed to reducing the overall number of astrocytes.

In addition to their effect on astrocytes and microglia, IL-6 and IL-1β can also act directly on neurons to alter brain plasticity. In fact, an intracranial infusion of IL-6 and administration of IL-1β into the hippocampus increases depression-associated behaviour and reduces neurogenesis. To alter brain plasticity, the cytokines can either act on serotonin neurons via the kynurenine pathway or directly on glutaminergic neurons in the frontal cortex and hippocampus.[16] Therefore, IL-6 and IL-1β antibodies can prevent cytokines from altering neuronal plasticity, thereby reducing the potential for development of depressive behaviour.

Various studies have demonstrated that the differences in the innate peripheral immune response can predict susceptibility or resilience to repeated social defeat stress (RSDS).[16] It has been observed that prior to stress exposure, animals that later became susceptible had a higher IL-6 count prior to stress. Furthermore, Hodes and colleagues demonstrated a causal relationship between IL-6 counts and RSDS susceptibility.[16] To do this, the team removed hematopoeitic stem cells (HSCs) from IL-6 +/+ and IL-6 -/- mice and transplanted these HSCs into wildtype mice that had their peripheral immune cells irradiated. The results showed that stress-susceptible IL-6 +/+ chimeras developed susceptibility to RSDS, whereas IL-6 -/- chimeras became resilient to RSDS.[16] Therefore, it is apparent that a dysregulated inflammatory response can induce susceptibility to RSDS and contribute to the development of depressive symptoms. As such, anti-IL-6 antibodies such as tocilizumab, which are currently FDA-approved for the treatment of inflammatory diseases like arthritis, can be considered for the symptomatic treatment of psychiatric diseases.[16] Similarly, current psoriasis therapeutic agents like anti-IL-12/23 antibodies (e.g. ustekinumab), and anti-IL-17A antibodies (e.g. secukinumab) have also been shown to reduce the prevalence and severity of depression.[17-21]

Future Outlook

Similar to the way in which psoriasis medications treat mood and anxiety disorders, psychoactive drugs have also been suspected to help treat psoriasis in patients. Reducing anxiety can reduce the release of stress compounds, thus reducing body's inflammatory reaction. In fact, stress signals such as CRH and substance P contribute to the release of inflammatory cytokines such as TNF-α and interleukins.1 Therefore, a potential avenue of exploration is to determine whether anti-anxiolytic medications can also be used for psoriasis management. It is yet to be determined whether these medications can help alleviate psoriatic symptoms, or whether they in fact aggravate psoriasis further. Thus, further examination of the interplay between stress and inflammation can shed further light on this matter.

Conclusions

Psoriasis provides evidence for the connection between the psychological symptoms caused by changes in the brain as well as cutaneous symptoms caused by changes in the skin. The bidirectionality of these interactions is used to alleviate mood and anxiety disorders with psoriasis medications. In particular, TNF-α blockers such as etanercept and infliximab can reduce depressive behaviour by inhibiting serotonin deprivation and HPA-axis modulation. In addition, anti-IL-1β and anti-IL-6 antibodies such as tocilizumab can reduce

anxiety and depression symptoms by inhibiting astrocyte and microglial modulation and by preventing cytokine-mediated alterations in brain plasticity. Future studies can aim at determining the efficacy of anti-anxiolytic medications for treatment of psoriasis.

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