



Neuromodulation in Psoriasis and Psoriatic Arthritis

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Abstract

Psoriasis and psoriatic arthritis are debilitating chronic diseases that can significantly impair quality of life. A wide array of effective novel medications have become available with increased understanding of the immunology of these diseases, but the role of the nervous system in psoriasis and psoriatic arthritis remains largely uncharacterized. However, psoriasis is widely recognized by patients and physicians as a stress-responsive disease, and stress-alleviation maneuvers have been shown to decrease the severity of psoriasis. Recent studies have demonstrated that vagus nerve stimulation can decrease inflammation in rheumatoid arthritis, a disease closely linked to psoriasis and psoriatic arthritis. In this paper, we discuss these recent findings of the role of the nervous system in decreasing inflammation in rheumatoid arthritis. Additionally, we will provide an overview regarding the pathophysiology of psoriasis and psoriatic arthritis and discuss how neuromodulation could translate to the treatment of patients with psoriasis and psoriatic arthritis.

Introduction

Psoriasis vulgaris (PsO) is a chronic immune-mediated systemic inflammatory disease that is characterized by well-demarcated erythematous plaques with overlying micaceous scale, affecting roughly 2% - 3% of the United States population [1,2]. PsO is associated with significant comorbidity, including depression [3-5], increased risk of cardiovascular events [6,7], diminished quality of life [8], as well as overall increased mortality [9]. Furthermore, up to 40% of patients with PsO have or will develop comorbid Psoriatic Arthritis (PsA) in their lifetime [10].

Much research has gone towards discovering the pathogenesis for both PsO and PsA, and developing treatments targeting the pathophysiological basis for these diseases. Despite this, there has been very little, if any, work done on the role of the nervous system in the treatment of PsO. There has however been some fledgling work done in the field of Rheumatoid Arthritis (RA), a disease that shares significant overlap in therapies with PsO, which has demonstrated efficacy in using neuromodulation as a treatment modality [11].

The focus of this paper will be to provide an overview of the role of the nervous system in inflammation, and additionally review neuromodulation in RA and how it can translate to the treatment of PsO and PsA.

The immunomodulatory reflex

One of the most exciting findings in recent years regarding the role of the nervous system in immunity was the discovery of the “immunomodulatory reflex”. In this reflex, activation of the vagus nerve plays an integral role in down regulating inflammation [12].

The “cholinergic anti-inflammatory pathway,” involves firing of vagus nerve efferents in an attempt to decrease inflammation. Stimulation of this efferent arm of the immunomodulatory reflex, resulting in increased cholinergic outflow, has been shown to decrease cytokine production by innate immune cells [12]. This pathway has been shown in various models to decrease the severity of inflammation in sepsis, colitis, pancreatitis, and various other inflammatory conditions [12].

Studies on the role of acetylcholine in inflammation have demonstrated that release of TNF, IL-1 β , IL-6, and IL-18 in lipopolysaccharide exposed human macrophage cultures was attenuated with cholinergic stimulation [13]. Furthermore, rat models demonstrated that electrical stimulation of the vagus nerve resulted in attenuation of the peak serum concentration of TNF, as well as decreased TNF synthesis in the liver of rats that were undergoing lethal endotoxemia [13]. These findings suggest that activation of the vagus nerve and its cholinergic efferents play a significant role in regulation of the immune response.

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Further research regarding the role of cholinergic receptors in inflammation have given further credence to the importance of a cholinergic cascade in modulation of the immune response. In particular, the $\alpha 7$ subunit of the nicotinic acetylcholine receptor ($\alpha 7$ nAChR), which is known to be widely expressed on immune cells, has been identified as a key component of the immune response. Demonstrating this, vagus nerve stimulation in wild-type mice resulted in attenuation of endotoxin-induced serum TNF levels, whereas the same decrease was not found in $\alpha 7$ nAChR-deficient mice [14]. In addition, $\alpha 7$ nAChR-deficient mice demonstrated significantly higher levels of TNF than wild-type mice in response to an endotoxin challenge [14-16]. These findings of impaired lowering of inflammatory cytokines in $\alpha 7$ nAChR-deficient mice implicate the cholinergic efferent arm of the vagus nerve as a critical part of the inflammatory response.

Neuromodulation: A useful modality in RA/The role of autonomic imbalance

Autonomic imbalance has been implicated as a key underlying feature of several inflammatory arthritides, including RA [17,18] and PsA [19]. This imbalance is skewed particularly in favor of the sympathetic nervous system in these illnesses, a result of parasympathetic nervous system dysfunction [18,20]. Findings that increased autonomic imbalance predicts diminished response to anti-TNF therapy in inflammatory arthritides [21], including RA and PsA, indicate that restoration of this balance could be key in improving efficacy of treatment for these diseases.

Given that autonomic imbalance is well-characterized in RA, increased research has gone into evaluation of targeting of the inflammatory reflex as a treatment modality. Using a mouse model for RA, Levine et al showed that mice that had received vagal stimulation presented with decreased bone erosion, cartilage destruction, and disease severity compared to non-vagally stimulated mice [22]. In addition, RANKL, a cytokine found at elevated levels in RA that contributes to bony erosion, was found to be significantly decreased in the group that received neurostimulation.

Koopman et al. [11] extended these findings, demonstrating that implantable vagus nerve stimulation improved RA disease severity in humans. In particular, this study noted that vagal nerve stimulation inhibited TNF, IL-1 β , and IL-6 production in humans, confirming the findings of the role of the inflammatory reflex from prior studies in animal models. Perhaps most importantly, positive clinical responses were found in patients who had failed prior methotrexate and biologic therapies, thus highlighting vagal nerve stimulation as a possible treatment for refractory RA.

Neuromodulation in PsO and PsA

Although neuromodulation is an exciting up-and-coming therapy being studied in RA, the role of neuromodulation in PsO and PsA remains largely unexplored. Given the similarity of these chronic inflammatory diseases, and the shared treatments commonly used for patients, the findings of vagal nerve stimulation being effective in decreasing RA disease severity presents an exciting new possibility for PsO and PsA treatments.

PsO: A pathophysiologic overview

The pathophysiology of PsO, while very complex, has been extensively studied, giving rise to a vast amount of literature detailing the changes in cytokine levels associated with this chronic inflammatory disease. This consequently has given rise to the

plethora of treatments available for management and treatment of PsO. Our current understanding of the cytokine profiles associated with the pro-inflammatory state of PsO suggest feasibility of using the immunomodulatory reflex to target key cytokines implicated in the pathogenesis of PsO.

Recent study has identified several key cytokines that are critical in the PsO pathway, such as IL-17 and IL-23, but the role of Tumor Necrosis Factor (TNF) remains perhaps the best characterized. TNF is well-known to be an inflammatory marker in various diseases, and has been found to be elevated in both serum and skin lesions in PsO patients. TNF plays a large role in the pathogenesis of the scaly, erythematous lesions seen in PsO, by inducing increased keratinocyte proliferation, increasing recruitment of inflammatory cells [23], increasing the production of various pro-inflammatory cytokines [24], and ultimately propagating a chronic inflammatory state. Additionally, serum concentrations of TNF- α have been shown to correlate with PsO disease activity [25], as measured by Psoriasis Area and Severity (PASI) score, and are reduced after successful treatment of PsO [25,26].

TNF- α is produced by a wide range of cells, including T cells, keratinocytes, macrophages, and dendritic cells, and plays a major role in inducing and maintaining a chronic inflammatory state in PsO. In the psoriatic inflammatory cascade, high levels of the pro-inflammatory cytokines TNF- α and IFN- γ activate myeloid dendritic cells. These activated myeloid dendritic cells, in turn, migrate to the lymph nodes and secrete IL-12 and IL-23, which promote naïve T-cell proliferation and differentiation into Th1 and Th17 cells respectively [27]. Th1 cells secrete TNF- α and IFN- γ , while Th17 cells secrete IL-17A and IL-17F, to activate keratinocytes.

Activated keratinocytes subsequently release several pro-inflammatory cytokines, including TNF- α , IL-1 β , and IL-6. These pro-inflammatory cytokines feed back onto this inflammatory cascade, resulting in a positive feedback loop, consequently promoting chronic inflammation.

Currently approved biologic treatments for PsO largely fall under two major categories: TNF- α antagonists and treatments targeting the IL-23/IL-17 axis. While IL-23/IL-17 targeted biologics - ustekinumab, guselkumab, tildrakizumab, and secukinumab - have demonstrated great efficacy in treating PsO, use of neuromodulation shares more similarity with the TNF- α antagonist subclass of biologic treatments.

Highlighting the critical role of TNF- α in the pathogenesis of PsO, three TNF- α antagonists are currently approved for the treatment of moderate-to-severe PsO: etanercept, infliximab, and adalimumab. Of these, infliximab is not commonly used for PsO patients due to its black box warning for increased risk of Hepatosplenic T Cell Lymphoma (HSTCL), seen in trials of inflammatory bowel disease patients [28]. However, etanercept and adalimumab are commonly preferred by some patients and physicians as first-line biologics, due to their relatively long tenure on the market as compared to other newer biologic agents. The long history of extensive use of these medications for other clinical indications allows for a better understanding of their long-term effects. Studies done in PsO with both etanercept [29,30] and adalimumab [31,32] have confirmed the excellent long-term safety of these TNF- α antagonists, supporting their extensive use in the dermatology community.

PsO: The role of stress

Additionally, stress is thought to play a large role in the

development of PsO, in both patient perception [33] and in systemic endocrine response.

Stress is commonly implicated by patients as a trigger for flare-ups of PsO in both survey studies [34] and in the clinical setting. Emotional stress does not act as a trigger for all patients, but certain patients appear to have disease that is “stress-responsive”. These patients classically present as more anxious patients with a long history of PsO, with flare-ups easily predictable and triggered with times of stress. The key role of stress in PsO is further supported by various findings of adjuvant psychodynamic treatments being effective in yielding positive outcomes in PsO. Psychotherapy, biofeedback, hypnosis, meditation, and emotional disclosure all demonstrated significantly improvement in the physical and psychological symptoms of PsO [35,36].

Furthermore, the important role of stress in PsO is also reflected with respect to the systemic response to acute stressors. Patients with PsO have been shown to demonstrate an inhibited Hypothalamic-Pituitary-Adrenal (HPA) axis response to social stress as compared to controls [37]. Interestingly, patients who self-identify as “stress-responsive” demonstrate lower baseline salivary cortisol levels, and lower serum cortisol levels after stressor stimuli as compared to PsO patients who did not identify as “stress responsive”. Patients reporting higher levels of daily stressors had lower mean cortisol levels in another subset of patients [38], corroborating the idea that dysfunction of the HPA axis may play a role in “stress-responsive” PsO patients. Given the known associations between the autonomic nervous system and the systemic stress response, modulation of the nervous system may provide a method of remodeling the HPA axis to help target aberrant feedback mechanisms in stress-responsive PsO patients.

PsO: Why neuromodulation should work

There likely remains a large portion of the pathophysiology of PsO which remains undiscovered, but our current understanding of the underlying pathogenesis of this disease and the mechanisms of current efficacious treatments indicate that neuromodulation could potentially be beneficial for treating PsO patients. Perhaps most promising is the study by Borovikova et al. Demonstrating attenuation of TNF, IL-1 β , and IL-6 levels in human macrophage cultures in response to cholinergic stimulation [13]. These pro-inflammatory cytokines are critical components of the psoriatic inflammatory cascade, each playing a key role in propagating the constant inflammation seen in PsO. Thus, using the inflammatory reflex for neuromodulation could work in a similar manner as TNF- α inhibitors to interrupt the chronic inflammatory cycle, and potentially treat PsO.

Additionally, the dysfunctional stress response seen in PsO, particularly with “stress-responsive” patients, identifies the closely-linked autonomic nervous system as a potential target for adjunct treatments. The promising findings in alternative therapies, such as meditation, hypnosis, and biofeedback illustrate the potential of relaxation in reducing symptoms of PsO. The exact mechanism of these methods has not been well studied, but we suggest that increased parasympathetic tone from these mindfulness activities may play a role in addressing the inflammatory mechanisms of PsO to alleviate symptoms. Neuromodulation can build off these findings, and involve stress-alleviating activities to increase parasympathetic tone for treatment and maintenance therapy for “stress-responsive” PsO.

PsA: A pathophysiologic overview

PsA is classified within the family of “inflammatory arthritides,” a designation shared by RA and ankylosing spondylitis. As such, it shares several pathophysiologic characteristics with both of these diseases, as well as PsO. Research into the underlying pathogenesis of PsA alone is increasing, but treatments for this disease have historically been based off of validated treatments for other inflammatory arthritides, namely RA. The pathophysiologic features in PsA shared with RA and PsO suggest that neuromodulation would be effective in treating its symptoms.

PsO precedes PsA by 10 years in 80% of patients [39], so patients often have concomitant skin disease at the time of presentation with joint symptoms. Thus, it is difficult to distinguish whether the pathogenesis of these diseases occurs *via* related or distinct mechanisms.

Like PsO, TNF- α plays a primary role in propagation and maintenance of a chronic inflammatory state in PsA [40]. As with TNF levels in skin lesions in PsO, TNF levels in the synovial fluid [41] and synovium [42] have been found to be significantly elevated, a phenomenon also seen in RA. Specifically with regard to the inflammatory arthritides, TNF is known to play a critical role in joint damage, promoting osteoclastic bone resorption and inhibiting bone collagen synthesis [43]. Additionally, TNF has been shown to promote synovial cell and dermal fibroblast production of collagenase and PGE2 [44], a known promoter of osteoclastic bone resorption in inflammatory disease [45].

Similar to PsO, the currently approved biologic treatments for PsA largely fall under the realms of IL-23/IL-17 axis targeted biologics (ustekinumab and secukinumab) and TNF- α antagonists. These treatments are indicated after failure of disease modifying anti-rheumatic drugs (DMARDs). DMARDs, such as methotrexate, are commonly used in clinical practice to treat PsA, despite a limited amount of data supporting their efficacy in PsA [46,47]. Interestingly, DMARDs have been shown to limit progressive joint damage in RA patients [48], but their disease-modifying effect in PsA remains under controversy. Although current literature demonstrates that DMARDs have minimal-to-no effect in attenuating joint damage in PsA [46], these therapies still remain a mainstay, and a first-line treatment after failure of NSAIDs, in the treatment of PsA [49].

In addition to the TNF- α antagonist therapies approved for PsO, two other TNF- α blockers, golimumab and certolizumab, are approved for the treatment of PsA. Contrary to DMARDs, TNF- α antagonists have been demonstrated to significantly slow joint damage in PsA patients [40,46]. The efficacy of TNF- α blockers in slowing disease progression gives credence to the essential role of TNF in promoting joint damage in this disease. TNF- α antagonists have also shown additional effectiveness in treating synovitis, skin symptoms, nail changes, enthesitis, dactylitis, and axial disease associated with PsA [50,51]. Thus, biologic treatment of PsA represents a key long term option for managing chronic disease and improving quality of life for patients.

Although TNF and the IL-23/IL-17 axis [52,53] are key targets for novel biologic therapies for PsA, several other cytokines are known to be key contributors to the pathogenesis of PsA. In particular, IL-1 β , IL-6, and IL-18 expression is elevated in the synovium in PsA as compared to RA [42]. Similar to PsO, these cytokines are key to propagating the positive feedback loop of the inflammatory cascade,

maintaining a chronic inflammatory state in patients suffering from this disease. Expression of Matrix Metalloproteinases (MMPs) [42] and RANKL [47] are also increased in both PsA and RA. The shared elevation of key cytokines and inflammatory markers in these inflammatory arthroses demonstrate that the pathogenesis of these diseases is very closely related.

PsA: Why neuromodulation should work

Although PsA has not been as thoroughly studied as RA, its similarities with both PsO and RA hint that neuromodulatory therapies may yield significant benefits in its disease management.

Historically, treatments for PsA have been built off of validation for treatments in RA. This model gave rise to the extensive use of DMARDs for PsA, despite limited evidence backing their efficacy, and has also resulted in the wide range of effective biologic therapies available for treatment of PsA now. The close relationship that PsA and RA share as members of the “inflammatory arthritis” family is backed by their similar responses to treatment and observed similarities in underlying pathophysiology.

As with PsO and RA, TNF- α inhibitors are mainstays of treatment for PsA, acting as a first-line biologic for worsening disease. The efficacy of these medications in not only reducing skin symptoms, but attenuating joint damage, axial disease, and enthesitis highlight the key role of TNF- α in triggering a multitude of symptoms in PsA. In conjunction elevated TNF- α levels, the elevated IL-1 β and IL-6 levels found in PsA synovial samples may act as markers of the known autonomic imbalance in PsA [19]. With reduction of these pro-inflammatory cytokines being a known result of cholinergic stimulation [13], neuromodulation presents a promising possibility for novel treatment of PsA.

In addition to maintaining appropriate levels of pro-inflammatory cytokines, perhaps the most important goal of therapy for inflammatory arthritis is reduction of joint damage. PsA patients demonstrate even lower quality of life than PsO patients [54], with joint pain being a major factor in impairing both emotions and function [51]. Thus, treatment of joint symptoms should be one of the foremost goals for physicians to improve these patients' quality of life. General inflammation, such as elevated TNF- α levels, certainly contributes to bony erosion, but several mechanisms cause joint breakdown in inflammatory arthritides. Specifically, increased levels of RANKL, an osteoclast activator, are known to be present in the joint space in both RA and PsA. However, the recent finding that vagus nerve stimulation in RA patients reduces RANKL levels and improves RA symptoms [11] provides an exciting new possibility that should be explored for treatment of PsA patients.

Neuromodulation: Benefits over biologics

While the majority of current research into treatments is currently being put into discovering more efficacious and safer biologic treatments for chronic inflammatory diseases, the promising results seen with Vagus Nerve Stimulation (VNS) in reducing disease severity in RA has potentially opened up a new field for researchers to explore. Treatments within the realm of neuromodulation could yield various benefits over current therapies, such as increased safety and increased cost-effectiveness.

With the average course of biologics alone for PsO ranging between \$22,000 and \$59,700 per year [55], there exists a large need for more affordable treatments for patients. Neuromodulation of the

vagus nerve offers a broad range of treatment options, from invasive procedures, such as implantable vagus nerve stimulators, to non-invasive methods, such as meditation [56] or carotid massage.

Even the most expensive of these, the implantable vagus nerve stimulator, costs roughly \$10,000 - \$24,000 [57-59], with the costs of implantation totaling around \$10,000, comparable to a year of biologic therapy. However, with battery lives of these implantable devices exceeding 10 years, the long-term costs of chronic disease could be drastically reduced with implementation of these therapies.

But for even the average patient, simple neuromodulatory techniques, such as vagal maneuvers, yoga, journaling, and practicing mindfulness, could offer low-cost or even free adjunctive therapies to help manage their PsO or PsA. The ability for the patient to engage in these treatment at their leisure, completely under their own control, could also serve to increase patient compliance, a known issue in dermatology [60].

Perhaps more importantly, neuromodulatory techniques have been well-studied for several decades and found to be relatively safe in their currently approved clinical indications for epilepsy, cluster headaches, and major depression.

The recent boom in discovery of biologics for PsO and PsA has assuredly been an exciting breakthrough in the field of dermatology, but hesitancy about possible long-term side effects from patients and prescribing dermatologists alike has hindered the widespread adoption of these therapies. The lack of data on the long-term effects of altering the immune response using biologic treatments remains worrisome to the dermatology community at large, and is unfortunately a worry that can only be quelled with time. On the other hand, no adverse effects have been associated with long-term use of VNS in clinical practice for its several clinical indications.

The most common side effects seen with implantable VNS include surgery-related infection or hemorrhage, incisional pain, hoarseness, pain, and dyspnea. These side effects are typically mild and well tolerated, associated with stimulation, and tend to improve with time [61]. Postoperative infections occur in 3% - 6% of VNS patients, but are easily treated with oral antibiotics, and rarely require explantation [61]. The tolerable short-term and favorable long-term safety profile of using the vagus nerve for neuromodulation could make it a useful, less fearsome treatment for PsO and PsA patients.

Future Directions

Breakthroughs in the importance of parasympathetic tone in the inflammatory response in the past 20 years have brought to light the importance of the nervous system in addressing immune dysfunction. The known autonomic imbalances seen in inflammatory arthritides give credence to the inflammatory reflex being an integral part of the pathogenesis of these diseases, which appears to be modifiable to patients' benefit by neuromodulation. Vagus nerve stimulation has shown great promise in RA as a potential treatment option, utilizing the inflammatory reflex to significantly reduce the severity of the chronic inflammatory disease.

Neuromodulation has not been as well studied in PsO or PsA, but the similarity of RA and these diseases in both pathogenesis and effective treatments suggest that neuromodulation could benefit these patients as well. The inflammatory reflex affects several pathways known to be essential in the pathogenesis of both PsO and PsA, with increased cholinergic outflow reducing pro-inflammatory cytokines

to maintain homeostasis within the immune response.

Thus, the inflammatory reflex could be utilized to target the chronic inflammatory states associated with both these diseases. Additionally, certain subsets of PsO patients, such as “stress-responsive” patients, demonstrate unique physiologic profiles, suggesting that they could receive increased benefit from treatments modulating their parasympathetic tone. The known aspects of the pathogenesis of PsO and PsA hint that modulation of the nervous system could play a role in reverting these patients’ immune systems to a more preferable state.

Future research should be conducted to investigate the immunologic profile of vagal nerve stimulation in PsO and PsA patients, and the efficacy of using neuromodulation to treat the symptoms and long-term effects of these chronic inflammatory diseases. A greater understanding of the intrinsic neuromodulatory pathways in PsO and PsA can help increase our understanding of the etiology and progression of these diseases, as well as develop novel treatments to help manage these burdensome chronic conditions.

Utilization of implantable vagal nerve stimulators for treatment may ultimately provide a safer, more cost-effective treatment compared to biologics for patients with these chronic diseases. With both patient and provider fears of the long-term side-effects of new biologic therapies, neuromodulation could provide a tried-and-tested option for PsO and PsA treatment, with minimal long-term side effects. Additionally, the broad range of maneuvers available that are known to affect parasympathetic tone open the door for possibilities for less-invasive therapies, such as mindfulness, meditation, and yoga, to play an adjunct role in managing and treating patients’ chronic disease. Combination therapy using neuromodulatory techniques or interventions with pharmacologic therapies may target PsO and PsA using 2 very different mechanisms of action, which may result in an additive or synergistic treatment effect to more effectively manage patients with these chronic diseases.

Although the fields of PsO and PsA have majorly benefitted from the constant stream of new biologic therapies coming onto the market in recent years, new findings in the field of neuromodulation have opened up an exciting new realm of possibilities for novel treatments for PsO and PsA. Further exploration into this promising field will help increase our understanding of these burdensome chronic diseases, and improve the treatment that we can provide for our patients.

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