REVIEW

Pumping Up Dermatologic Drug Reformulation: A Review of How Proton Pump Inhibitors May Revolutionize Scleroderma Treatment

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Scleroderma is a rare and often debilitating connective tissue disorder of unknown etiology affecting the skin, lungs, and other visceral organs. Current medical therapies are limited and largely focused on symptoms, particularly in advanced disease. Recent preclinical studies have shown that topically reformulated proton pump inhibitors (PPIs) reduce inflammation and fibrosis, suggesting therapeutic potential in scleroderma. In this article, we explore the emerging role of PPIs as an adjuvant therapy in scleroderma. We also describe the key mechanisms of scleroderma and current therapeutic options and highlight how PPIs modulate molecular pathways central to fibrotic disease. **KEYWORDS:** Proton pump inhibitors, scleroderma, fibrosis, drug repurposing, drug development

Scleroderma is a rare, chronic autoimmune skin disease characterized by excessive fibrosis, vasculopathy of the skin, and inflammation.[1] There are 2 major types of scleroderma depending on disease involvement and severity. Localized scleroderma only affects the skin and subcutaneous tissue, while systemic scleroderma (SSc) involves the skin and internal organs.[2] Localized scleroderma is further divided into morphea, linear scleroderma, and scleroderma en coup de sabre, while SSc is classified as limited systemic sclerosis (CREST syndrome) or diffuse systemic sclerosis based on specific clinical and diagnostic criteria.[3] Scleroderma often coincides with other rheumatologic diseases, suggesting significant immune involvement.[3]

The exact mechanisms of scleroderma are unknown. Disease pathogenesis is thought to be driven by a combination of hereditary and environmental factors that trigger an aberrant immunologic response, leading to an increase in inflammatory cells, endothelial cell dysfunction, and uncontrolled fibroblast proliferation.[1,4] Additionally, several studies have shown that scleroderma disease progression involves multiple interconnected molecular pathways rather than a single, well-defined process, making them promising targets for drug development.[5]

In recent years, proton pump inhibitors (PPIs) have emerged as a promising therapeutic candidate for scleroderma. PPIs demonstrated antifibrotic effects through their known antioxidant and anti-inflammatory properties, showing utility in treating fibrosis of the liver, gastrointestinal tract, lungs, and skin.[6] Several preclinical models have shown that the PPI esomeprazole, when topically reformulated, significantly suppressed lung inflammation and subsequent fibrosis in vivo and in vitro by inducing the mitogen-activated protein kinase (MAPK), nuclear factor erythroid 2-related factor 2 (NRF-2), and heme oxygenase 1 (HO-1) pathway and inhibiting the dimethylarginine dimethylaminohydrolase (DDAH) and nitric oxide synthase (NOS) pathway.[7–10] Additionally, esomeprazole has been shown to synergistically enhance the antifibrotic efficacy of pirfenidone through complementary molecular mechanisms.[11] Together, these findings suggest that PPIs may be repurposed as adjunctive therapy in fibrotic diseases such as scleroderma where treatment options remain limited.

The purpose of this review is to highlight the potential beneficial impact of PPIs in scleroderma treatment while also considering the current therapeutic landscape in this patient population, ultimately aiming for better patient outcomes. In this review, we describe the molecular pathways by which PPIs could modulate processes central to scleroderma pathogenesis, including vascular dysfunction, inflammation, and oxidative stress.

KEY MECHANISMS IN SCLERODERMA

Scleroderma is a complex autoimmune disorder with a multifaceted pathogenesis characterized by 3 main hallmarks: vascular dysfunction, autoimmunity, and progressive fibrosis.[3] While several triggers such as viruses, environmental exposures, autoantibodies, and inflammatory cytokines are linked to disease etiology, genetic susceptibility plays a significant role in the immune response, determining disease severity and

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progression.[12] Regardless of the initial insult, aberrant activation of fibroblasts, leading to excessive extracellular matrix deposition with thrombotic and fibrinolytic cascade activation, contributes to the characteristic tissue damage seen in scleroderma.[13]

Vascular dysfunction plays a crucial role in the pathogenesis of SSc, with early endothelial cell damage triggering several profibrinogenic signaling pathways.[14] The endothelial layer and surrounding tissue regulate vascular architecture, smooth muscle growth, cellular adhesion, and inflammation via several potent chemokines.[15] For example, tissue hypoxia within the endothelial layer and aggravated vascular damage lead to imbalanced levels of vascular endothelial growth factor and endothelin-1, disrupting angiogenic signaling and promoting the persistent endothelial dysfunction seen in SSc.[16] Cell adhesion molecules also play a role in the stability of endothelial cells, and their increased expression has been linked to the initial phases of SSc pathogenesis. More specifically, elevated levels of E-selectin, vascular cell adhesion molecule-1, and intracellular cell adhesion molecule-1 are correlated with poorly regulated angiogenesis, aberrant activation of endothelial cells, and persistent vascular impairment, leading to SSc development and progression.[17–22]

Additionally, circulation of damaged endothelial progenitor cells could also contribute to the vascular deterioration seen in SSc.[23] Abnormal expression of 2 transcription factors, Fos related antigen 2 (Fra2) and Friend leukemia virus integration 1 (Fli1), have been associated with SSc vasculopathy and tissue fibrosis.[24-30] Both transcription factors regulate genes essential in vascular maturation and stabilization. High levels of Fra2 expression are linked to inflammation, with severe remodeling of the vasculature resulting in obliteration and fibrosis.[24] Conversely, reduced expression of Fli1 may contribute to structurally unstable blood vessels that are prone to rarefaction and regression.[24]

Inflammation and immunologic dysregulation are also important mediators in the pathophysiology of SSc.[31] T-lymphocyte and macrophage infiltration is observed in scleroderma-affected tissues as a result of immune cell activation and proinflammatory cytokine release in response to various triggers, including genetic predisposition and environmental factors.[3] This is supported by the increased levels of fibrogenic cytokines, such as tumor necrosis factor α (TNF-α), interleukin (IL) 1, and IL-6, being found in patients with SSc.[32-34] Also, overexpression of toll-like receptor (TLR) 2 and TLR4 has been reported in the fibroblasts and skin of individuals with SSc.[35,36] Taken together, these findings suggest a major role for the innate immune system in the chronic inflammatory state of SSc. PPIs are a promising new treatment option because of their ability to modulate many of these mechanisms.

CURRENT THERAPEUTICS FOR SCLERODERMA

Medical management of scleroderma remains challenging and is often patient-specific and governed by extracutaneous manifestations as well as the extent of fibrosis.[37] Immunosuppressive therapies such as corticosteroids, cyclosporine A, mycophenolate mofetil, azathioprine, methotrexate, and cyclophosphamide are the standard-of-care pharmacotherapy for scleroderma, especially during the initial inflammatory stage.[38] These drugs limit the inflammatory stage of the disease and reduce fibrosis but are associated with an increased risk of infection and organ toxicity with prolonged use.[39] Moreover, their utility is often limited to the initial stages of the disease course before irreversible fibrotic remodeling occurs.[38] More intensive therapies such as autologous hematopoietic stem cell transplantation may be considered in patients with severe disease, but its use should be limited due to substantial risks.[40]

In addition to systemic treatment, effective symptomatic management is essential for scleroderma. For example, vasodilators are often used to manage the vascular complications associated with scleroderma. Exaggerated and painful vasospasms of blood vessels, or Raynaud's phenomenon (RP), is a common complication of scleroderma and can result in diminished blood flow and skin discoloration.[41] Calcium channel blockers are frequently used to manage RP in patients with SSc and persistent digital ulcers.[41] Endothelin receptor antagonists are also used as disease modifiers in systemic sclerosis and have been shown to treat RP and digital ulcers.[42,43] Similarly, phosphodiesterase type 5 inhibitors have been shown to treat SSc-related vasculopathy.[44,45] Symptom treatment plays a critical role in improving patient quality of life and satisfaction; however, it does not provide benefit to patients with advanced fibrosis and irreversible organ damage.

Preventing and treating fibrosis is also a critical step in the management of SSc. Antifibrotic therapies have been shown to decrease symptoms in patients with SSc, especially those with SSc-related interstitial lung diseases, but are often reserved for extensive disease and those whose symptoms progress despite immunosuppressive therapy.[46,47] The quest for novel therapeutics that attenuate the fibrotic process is potentially one of the most dynamic domains of scleroderma research, given the contribution of fibrosis to the disease process and the multifaceted drug discovery approach. More specifically, current approaches include the direct inhibition of fibroblast overproliferation and collagen production, targeting cytokines that activate fibroblasts into myofibroblasts, and the use of agents that facilitate accelerated breakdown of collagen within affected tissues.[48] In this regard, targeted transforming growth factor β (TGF-β) inhibition with fresolumumab, a novel isoform-selective TGF-β inhibitor, has been shown to decrease dermal myofibroblast infiltration in patients with early, diffuse cutaneous SSc.[49] Taken together, mechanism-based therapies that interrupt the fibrotic cascade may offer hope for more effective, long-term treatments in the future.

EMERGING ROLE OF PPI IN SCLERODERMA TREATMENT

PPIs have been used in the management of esophageal and gastric complications of SSc. Upper gastrointestinal tract dysfunction, such as gastroesophageal reflux disease, is common in those with SSc, making the empiric use of PPIs beneficial in this patient population. PPIs such as esomeprazole have also been shown to be therapeutically effective as antioxidant molecules against liver and lung fibrosis. The antioxidant activity of esomeprazole is thought to be through direct regulation of the MAPK/NRF-2/HO-1 pathway.[50] This could make PPIs an attractive option for investigation as a potential adjunct therapy for scleroderma, a disease characterized by significant increase in prooxidant molecules and decreased antioxidant activity.[51] Intriguingly, recent studies have demonstrated that topically reformulated esomeprazole efficiently controls scleroderma by lowering the oxidative stress induced by bleomycin both in vitro and in vivo in murine models.[52] The mechanism of action was

attributed to a reduction in the production of reactive oxygen species, a hallmark inflammatory driver in SSc pathobiology. It was also shown that esomeprazole favorably regulates several genes involved in wound pathobiology, making it a strong candidate for treating scleroderma.

Additionally, topically reformulated esomeprazole, coined dermaprazole, has been shown to decrease dermal inflammation in an animal model of ionizing radiation-induced dermatitis.[10] In this study, dermaprazole use was associated with the induction of the cytoprotective molecules HO-1 and NRF-2 to relieve the skin tissue from oxidative stress induced by ionizing radiation. Remarkably, administration of dermaprazole was shown to significantly reduce inflammation, epidermal thickening, parakeratosis, ulceration, and necrosis. In addition, dermaprazole reduced collagen accumulation and fibrosis by downregulating the profibrotic DDAH/NOS pathway. Collectively, these findings highlight the functional utility PPIs may have in treating fibrotic diseases in general and scleroderma in particular.

CONCLUSION

Given its efficacy in reducing tissue inflammation and fibrosis in preclinical models, PPIs are a promising new treatment frontier in scleroderma. Clinical data directly supporting PPIs as a disease-modifying agent in SSc are currently limited, and subsequent research is necessary to establish its safe and effective use in this patient population. While current treatment options effectively minimize disease burden, new adjunct topical therapies have the potential to improve patient quality of life and satisfaction.

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