Advancements in targeted therapies for scleroderma: navigating the complexities of systemic and localized disease management

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Abstract.
Background: Scleroderma, encompassing systemic sclerosis (SSc) and localized scleroderma (LoS), presents complex challenges due to its multifaceted pathophysiology and clinical manifestations. Targeted therapies have emerged as promising interventions, addressing specific pathways implicated in scleroderma pathogenesis. Methods and Materials: A systematic literature review was conducted following SANA guidelines, focusing on randomized controlled trials, observational studies, and systematic reviews evaluating targeted therapies in SSc and LoS. Inclusion criteria encompassed studies investigating immunomodulatory agents, antifibrotic drugs, and vasodilators, reporting clinical outcomes and safety profiles. Objectives: This review aimed to analyze the efficacy, safety, and mechanisms of action of targeted therapies in scleroderma subtypes, highlighting advancements in treatment paradigms. Discussions: Targeted therapies in SSc predominantly
target vascular dysfunction, fibrosis, and immune dysregulation, with promising results observed for biological agents and hematopoietic stem cell transplantation. In LoS, antifibrotic and anti-inflammatory agents have shown efficacy in skin fibrosis reduction. Emerging therapies, including JAK-STAT inhibitors and monoclonal antibodies, hold potential in both subtypes. Overall, targeted therapies herald a new era in scleroderma management, emphasizing personalized and effective interventions for improved patient outcomes.

**Keywords:**
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INTRODUCTION

Scleroderma is a connective tissue disorder characterized primarily by the thickening and hardening of the skin. The combining form “sclero” means "hard" in Greek, and the word “dermis” means skin [1].

Scleroderma affects approximately 20 new patients per million per year. Its pathophysiology is complex and involves early endothelial damage, an inflammatory infiltrate, and a resulting fibrotic reaction [2].

There are two major clinical subsets of scleroderma:

a. systemic sclerosis (SSc) is a complex systemic autoimmune disorder involving the skin multiple internal organs and

b. localized scleroderma (LoS), also known as morphea, is confined to the skin and/or subcutaneous tissues [3].

Current treatment modalities in SSc have focused on targeting vascular damage, fibrosis, and regulation of inflammation and autoimmune responses. Some drugs previously used in an attempt to suppress fibrosis, like D-penicillamine (D-Pen) or colchicine, have been disappointing in clinical practice despite anecdotal evidence of their advantages. Some canonical medications, including glucocorticoids, immunosuppressants, and vasodilators, have successfully treated various manifestations in SSc patients. Increasing evidence suggests that some biological agents targeting collagen, cytokines, and cell surface molecules might have promising therapeutic effects in SSc. In recent years, hematopoietic stem cell transplantation (HSCT), mostly autologous, has made great progress as a promising treatment option in severe and refractory SSc. Due to the complexity and heterogeneity of SSc, there are currently no optimal treatments for all aspects of the disease.

As for LoS, local skin-targeted therapy is generally used, including topical application of glucocorticoids or other immunomodulatory ointments and ultraviolet (UV) irradiation. In addition, systemic immunosuppressants are also utilized in several forms of LoS [3].

Localized scleroderma, also known as morphea, presents as localized inflammatory patches and skin fibrosis, constituting a rare but challenging aspect of connective tissue diseases (CTDs) [1, 2]. The etiology of morphea remains
elusive, with proposed mechanisms implicating genetic predisposition coupled with environmental triggers such as infections, trauma, and medications, culminating in immune dysregulation and chronic inflammation [1, 3].

The advent of targeted therapies heralds a promising era in addressing the specific underlying causes of scleroderma subtypes. These therapies can be broadly classified into antifibrotic, anti-inflammatory, and dual antifibrotic-antiinflammatory agents, each targeting distinct pathways implicated in scleroderma pathogenesis [4, 5]. For instance, antifibrotic agents like fresolimumab and imatinib target transforming growth factor-beta (TGF-β) signaling, a pivotal pathway in fibrosis development [5, 6]. On the other hand, anti-inflammatory agents such as tocilizumab and abatacept focus on modulating cytokine responses and immune cell activation [7, 8].

Systemic scleroderma, characterized by widespread fibrosis and multi-organ involvement, poses significant challenges in therapeutic interventions. Recent advancements have shifted the treatment paradigm towards targeted therapies that aim to disrupt specific biological pathways implicated in scleroderma pathophysiology [9, 10]. These pathways include endothelin-1-mediated vascular dysfunction, B and T lymphocyte dysregulation, and aberrant activation of profibrotic cascades [11, 12].

This manuscript segment delves into the diverse landscape of targeted therapies for localized and systemic scleroderma, exploring the mechanisms of action, clinical efficacy, safety profiles, and potential adverse effects associated with these novel therapeutic approaches. By unraveling the intricacies of targeted interventions, this manuscript aims to contribute to the evolving narrative in scleroderma management, emphasizing personalized and targeted strategies for improved patient outcomes and quality of life.

**METHODOLOGY**

A research question was created using the PICO framework. The studies identified through a systematic search were comprehensively read to assess their appropriateness for incorporation into the review based on the following criteria.

**Inclusion Criteria**

1. Population
Individuals diagnosed with scleroderma, including various subtypes such as limited cutaneous systemic sclerosis, diffuse cutaneous systemic sclerosis, etc.

Age range: Include both adult and pediatric populations if applicable.

No restrictions based on gender or ethnicity.

**Intervention/Exposure**

Studies investigating targeted therapies specifically designed to address the underlying causes of scleroderma subtypes

- Types of targeted therapies include but are not limited to immunomodulatory agents, anti-fibrotic drugs, vasodilators, genetic therapies, etc.

- Both monotherapy and combination therapy studies are included.

2. **Study Design**

- Randomized controlled trials (RCTs), non-randomized controlled trials, observational studies (cohort studies, case-control studies), and case series that provide relevant data on targeted therapies.

- Systematic reviews and meta-analyses focusing on targeted therapies in scleroderma subtypes.

3. **Outcomes**

- Studies reporting clinical outcomes such as improvement in skin fibrosis, lung function (e.g., forced vital capacity), quality of life assessments (e.g., SF-36, DLQI), survival rates, and disease progression markers.

- Studies assessing biomarkers or surrogate markers of disease activity or response to targeted therapies.

- Safety and adverse effect profiles of targeted therapies.

**Exclusion Criteria**

1. **Population**

- Studies exclusively involving populations with scleroderma-related conditions other than the specified subtypes (e.g., localized scleroderma, overlap syndromes).

- Studies focusing solely on animal models of scleroderma without direct relevance to human populations.

2. **Intervention/Exposure**

- Studies on non-targeted therapies or conventional treatments without a specific focus on addressing the
underlying causes of scleroderma subtypes.

- Herbal remedies, alternative medicine, or complementary therapies without clear mechanisms of action targeting scleroderma pathophysiology.

3. Study Design

- Case reports with limited generalizability or small sample sizes.
- Editorials, commentaries, letters to the editor, and opinion pieces without original research data.

4. Outcomes

- Studies lacking relevant outcome measures related to scleroderma subtype-specific improvement, disease progression, or safety profiles of targeted therapies.
- Studies with incomplete or insufficient data for analysis or interpretation.

The manuscript has been drafted based on SANRA guidelines to search, compile, contemplate, and extract data. Investigators independently searched PubMed, and Google Scholar following the protocol mentioned in the literature.

LOCALIZED SCLERODERMA

Localized scleroderma or morphea, is a rare chronic connective tissue disease (CTD) manifesting in the form of inflammatory patches and/or skin fibrosis [4, 5]. The exact pathogenesis of morphea is unknown, however, it is postulated that when genetically predisposed individuals are exposed to certain triggers such as infections, trauma, and drugs, it leads to immune dysregulation and inflammation.

Cytokines such as interleukin (IL)-4 and transforming growth factor-beta (TGF-β) can result in skin fibrosis [4, 6]. The chronic relapsing-remitting course of this disease, systemic complications, significant cosmetic, physical, and mental comorbidities, and the lack of a permanent cure underscore the need for specialized, targeted therapeutic interventions for morphea control [4, 5].

Targeted therapies for localized scleroderma can be classified into the following broad types: antifibrotic, anti-inflammatory, and dual antifibrotic-antiinflammatory agents [4, 5].

Antifibrotic agents such as fresolimumab and imatinib target TGF-β signaling to inhibit fibrosis [5]. Fresolimumab
was found to improve modified Rodnan skin score (MRSS), decrease dermal myofibroblast infiltration, and reduce the expression of TGF-β related genes in the skin in patients of systemic sclerosis (SSc) [7].

This may be a promising treatment for morphea as well. Imatinib, a BCR-ABL1 tyrosine kinase inhibitor, is currently undergoing a clinical trial in patients with severe cutaneous scleroderma. Imatinib may inhibit both TGF-β and platelet-derived growth factor receptor (PDGFR) to reduce skin fibrosis [5]. Connective tissue growth factor (CTGF) is targeted by antifibrotics such as iloprost and pamrevlumab [8]. Iloprost was found to reduce the dermal interstitial fluid levels of CTGF in patients of scleroderma as compared to healthy controls and can thus reduce skin fibrosis in morphea [9]. Pamrevlumab was found to reduce the expression of PDGFRβ and procollagen in dermal cells leading to decreased CTGF-mediated fibrosis. It was also found to decrease CTGF-mediated vascular injury [10].

Topical 8% pirfenidone gel can reduce TGF-β gene expression in dermal fibroblasts of morphea patients. It has been shown to improve modified Localized Scleroderma Skin Severity Index (mLoSSI) scores (p=0.002), durometer values (p=0.05), and histopathological pictures at 6 months [11].

Anti-inflammatory agents in morphea have various targets including cytokines, T-cells, and B-cells [5]. IL-6 and oncostatin M (OSM) are thought to be involved in fibrosis in morphea [5]. Tocilizumab, an agent targeting the IL-6 receptor (IL-6R), has shown a good clinical response in both adult and pediatric patients of morphea [12, 13]. Sarilumab, another IL-6R monoclonal antibody, is currently under trial for its use in morphea [8]. A National Health Service (NHS) evidence review of three case series that explore the use of abatacept, a T-cell costimulation inhibitor, in adult patients with severe, progressive morphea found that abatacept can result in disease activity reduction and functional improvement. There were also notable improvements in MRSS and Localised Scleroderma Cutaneous Assessment Tool (LoSCAT) scores with no serious adverse effects being reported [14].

Morphea patients have been found to have elevated levels of IL-2 receptors and increased expression of CD25 on T- and
B-cells. Basiliximab, a monoclonal antibody targeting CD25, has been shown to significantly decrease skin thickness in SSc patients [15, 16]. B-cell depletion therapy via rituximab, an anti-CD20 monoclonal antibody, has been found to improve skin scores at 24 weeks of use, skin myofibroblast numbers, and skin hyalinised collagen content [17, 18].

Dual antifibrotic-antiinflammatory agents include janus kinase-signal transducer and activator of transcription (JAK-STAT) inhibitors [5]. The JAK-STAT cascades play critical roles in inflammation-driven fibrosis. The activation of these pathways is through profibrotic cytokines and growth factors, OSM, ILs, and interferons. STAT3 plays a key role in TGFβ-induced myofibroblast differentiation and collagen synthesis [5]. Oral ruxolitinib, a JAK1 and JAK2 inhibitor, has been found to completely resolve skin lesions in patients with disabling pansclerotic morphea within 18 months of treatment [19]. A case study has found topical ruxolitinib 1.5% to be effective in morphea [22]. Baricitinib, a JAK1 and JAK2 inhibitor, has shown good results in two patients with morphea [21, 22]. Tofacitinib, a JAK1 and JAK3 inhibitor, has also been found to improve clinical pictures in morphea cases [23, 24].

**SYSTEMIC SCLERODERMA**

Recent advances have now led us to switch to target-based therapy, such as focusing on biological pathways, including cancer. This helps patients live a quality life and improves patient outcomes [25]. The pathogenesis of scleroderma involves the transforming growth factor-beta pathway, which affects fibrosis and tissue remodeling [26]. Targeted therapy for scleroderma may target endothelin-1, which causes vascular dysfunction, and B and T lymphocytes [26]. Recently, mechano-therapeutics for fibrotic illnesses, such as scleroderma, have gained popularity, the abnormal accumulation of collagen, which plays a role in fibrosis, is suppressed by reducing mechanical stresses, and that's how tissue fibrosis is reduced [27]. Additionally, the matrix metalloproteinase/tissue inhibitor system has been discovered as a prospective therapeutic target for scleroderma [28].

Therapeutic effects of tofacitinib showed downregulation of IFN-regulated gene expression on the epidermis, and it
also inhibited the STAT3 pathway, which lowered inflammation and the immunological response. Tofacitinib was well tolerated [29]. Anti-oncostatin M monoclonal antibodies target oncostatin, which affects inflammation and fibrosis (tissue scarring). This investigation demonstrated that patients who received 300 mg experienced adverse effects, whereas patients who received 100 mg did not, indicating that dose-dependent adverse effects were observed. Although not much improvement was seen in the disease prognosis [30].

Botulinum toxin A plays its role in Raynaud's phenomenon, by relieving vasospasm and establishing the recirculation and healing of digital ulcers. The study found that when botulinum toxin A was directly injected into the palmer digital neurovascular bundle, even greater doses were tolerated [31]. A retrospective study using Abatacept found that it prevented CD28 binding and lowered T-cell activation, resulting in less joint involvement and skin fibrosis [32].

Blinatumomab IV infusions suppress B cells, and not much effect is seen on T cell levels.

Two cycles of IV infusions were tolerated excellently, which helped reduce inflammation and fibrosis [33]. Inebilizumab (anti-CD19 monoclonal antibody) causes B cell depletion through antibody-dependent, cell-mediated cytotoxicity [35]. Rituiximab (anti-CD20 monoclonal antibody): Depletes B lymphocytes, which may improve lung function and skin fibrosis. It is generally well tolerated. [34]

Brentuximab vedotin (CD30 Targeting): Targets active immune cells, specifically lymphocytes that express CD30.

Imatinib and Nilotinib (tyrosine kinase inhibitors) inhibit tyrosine kinases, which may reduce skin thickness. QT prolongation was observed. Brentuximab vedotin (Targeting CD30): Targets active immune cells that express CD30. Inebilizumab (anti-CD19 monoclonal antibody) causes B cell depletion by antibody-dependent, cell-mediated cytotoxicity and is well tolerated [34].

There are various drugs that are being used for scleroderma treatment, but only a few well-designed studies have been performed to evaluate the safety profile and adverse effects of the drugs. Some of the drugs include immunosuppressing drugs such as methotrexate, mycophenolate...
mofetil, and cyclophosphamide. A major area of current research is the use of aggressive immunosuppressive therapy either with very-high-dose cyclophosphamide or with autologous bone marrow transplantation. Because these aggressive forms of immunosuppressive therapy have potential risks, they should be used in severe cases of scleroderma and administered as part of a research protocol.

In one study, hematuria, leukopenia, and anemia are the adverse effects seen in patients treated with cyclophosphamide for Systemic sclerosis-related ILD [35]. In another study, Fluid retention leading to lower limb edema occurred as an adverse event in a few patients on zibotentan, and none on a placebo [36]. Most patients developed headaches and gastrointestinal adverse effects (comprised of abdominal pain, diarrhea, and nausea) of mild or moderate severity, consistent with the known adverse effect profile of treprostinil [37].

Abatecept was generally found to be safe with a lower number of patients experiencing AEs compared to the placebo group [38]. Tocilizumab for SSc has been positively reported as safe. In the FocuSSced study, infections, cardiac diseases, and skin diseases were identified; meanwhile, the FocuSSced study demonstrated no major changes in the safety profile [39]. In patients with SSC-ILD, diarrhea was the most common adverse event, leading to discontinuation or dose reduction of nintedanib [40, 41, 42]

Mycophenolate mofetil was well-tolerated, with only 5% ceasing the drug because of adverse events such as severe diarrhea and recurrent infections [43].

One study demonstrated that autologous hematopoietic stem cell transplantation using high-dose cyclophosphamide, rbATG, and reinfusion of CD34-selected cells was associated with early treatment-related deaths but better long-term event-free survival (the primary outcome measure) and better overall survival at a median of 5.8 (interquartile range, 4.1–7.8) years’ follow-up compared with intravenous pulse cyclophosphamide for patients with diffuse cutaneous systemic sclerosis. HSCT was associated with more adverse events including respiratory distress, possibly due to rbATG and 10.1% treatment-related mortality, viral infections, and a
modest decrease in creatinine clearance [44].

**DISCUSSION**

The results of this review highlight the dynamic landscape of targeted therapies for scleroderma, spanning antifibrotic, anti-inflammatory, and dual antifibrotic-antiinflammatory agents. In systemic sclerosis (SSc), treatment strategies are multifaceted, targeting vascular damage, fibrosis, inflammation, and autoimmune responses. Traditional modalities such as glucocorticoids, immunosuppressants, and vasodilators have demonstrated efficacy in managing various manifestations of SSc. However, their use is often limited by adverse effects and suboptimal long-term outcomes.

Recent advances have introduced a paradigm shift towards biological agents and innovative therapies like hematopoietic stem cell transplantation (HSCT), particularly in severe and refractory cases of SSc. Biological agents targeting collagen, cytokines, and cell surface molecules show promise in modulating disease activity and improving patient outcomes. HSCT, predominantly autologous, has emerged as a promising treatment option, although its widespread adoption is hindered by logistical challenges and safety concerns.

In contrast, localized scleroderma (LoS) treatment primarily involves localized skin-targeted therapies and systemic immunosuppressants in select cases. The therapeutic landscape for LoS is less explored compared to SSc, with a focus on mitigating skin fibrosis and inflammation. Emerging therapies targeting specific pathways such as TGF-β signaling, CTGF-mediated fibrosis, and inflammation-driven fibrosis pathways offer novel avenues for LoS management.

Antifibrotic agents like fresolimumab, imatinib, and pirfenidone demonstrate the potential to reduce skin fibrosis and improve clinical outcomes. These agents target key mediators of fibrosis, aiming to halt or reverse the pathological processes driving tissue remodeling. Similarly, anti-inflammatory agents such as tocilizumab, abatacept, and rituximab show efficacy in dampening inflammatory responses and improving skin scores in patients with scleroderma.

Dual antifibrotic-antiinflammatory agents, notably Janus kinase–signal transducer and activator of transcription (JAK–STAT) inhibitors, present a promising approach to simultaneously target fibrosis and inflammation pathways.
Agents like ruxolitinib, baricitinib, and tofacitinib have demonstrated efficacy in reducing skin lesions and improving clinical parameters in scleroderma patients.

While these targeted therapies offer potential benefits, their safety profiles reveal varying degrees of adverse effects, underscoring the importance of personalized treatment approaches and vigilant monitoring. Further research is warranted to elucidate the long-term efficacy, optimal dosing regimens, and predictive biomarkers to guide treatment decisions in scleroderma. The evolving landscape of targeted therapies holds promise in improving patient outcomes, enhancing quality of life, and advancing the management of scleroderma across its diverse clinical manifestations.

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