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**Review Article**

# An Overview on Scleroderma

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**Abstract:** Scleroderma (systemic sclerosis), a complex illness, include severe fibrosis, vascular changes, and autoantibodies against several cellular antigens. Incidence rates range from 2.7 cases per million annually during 1947-1968 to 18.7 cases per million annually during 1972-1982. Prevalence estimates in the United States have also fluctuated, ranging from 138 cases per million during 1950-1979 to 286 cases per million in 1985. Though the exact cause of systemic sclerosis is not known, it is widely believed that both hereditary and environmental factors like parvovirus B19, Epstein-Barr, HLA DRB1*1104 and DQB1*0301 virus play a role in its development. The generally accepted classification of scleroderma is divided into two main subgroups: diffuse cutaneous scleroderma and restricted cutaneous scleroderma. Systemic sclerosis was often thought to be a dull fibrotic process, but there is now strong evidence that the pathophysiology of the disease involves an active inflammatory process. The majority of part of systemic sclerosis is determined clinically. When making a differential diagnosis, it is important to take into account a number of different illnesses that can resemble systemic sclerosis. The disease's normal progression cannot be changed by a conclusive treatment or generally accepted disease-modifying substance. Nonetheless, controlling the impacted system or systems has worked well. For better results, early diagnosis is essential. The effectiveness of treatment depends on clinical assessment, organ identification, and disease progression. In order to maximize the quality of life for impacted patients and stop more organ damage.

**Keywords:** Borelli Burgdoferi, Fibrosis, L-tryptophan, Mycophenolate, Parvovirus B19, Sclerodactyly.



## 1. INTRODUCTION

Scleroderma (systemic sclerosis), a complex illness, include severe fibrosis, vascular changes, and autoantibodies against several cellular antigens. The generally accepted classification of scleroderma is divided into two main subgroups: diffuse cutaneous scleroderma and restricted cutaneous scleroderma. Fibrosis in limited cutaneous scleroderma primarily affects the face, hands, and arms. Pulmonary hypertension is common, Anticentromer antibodies are found in between 50 and 90 percentage of patients, and Raynaud's phenomenon persists for years before fibrosis manifests. A fast developing condition that involves a significant portion of the skin and jeopardizes one or more internal organs is diffuse cutaneous scleroderma. Despite

improvements in the management of these implications, it is still unknown what processes underlie visceral involvement in scleroderma. Since the majority of the material that is currently available comes from cross sectional research & in individuals various states of the disease, occasionally after treatment, there is a dearth of pertinent data on processes. In addition, there are currently no adequate animal models of scleroderma. However, a thorough assessment of the available clinical and experimental evidence will assist to clear up any confusion and could serve as the basis for further scleroderma research [1]. Improvement in the management of these implications, it is still unknown what processes underlie visceral involvement in scleroderma. Since the majority of the material that is currently available comes from cross-sectional research and in individuals. We think that the abbreviation CREST (calcinosis, Raynaud's phenomenon, esophageal motility dysfunction, sclerodactyly, and telangiectasia) is no longer appropriate because it does not accurately reflect the burden of internal organ involvement and cannot be applied to a single subgroup of patients. Rarely people with scleroderma don't have any visible skin involvement. An overlap syndrome is thought to exist in patients who have scleroderma along with signs of Sjögren's syndrome, rheumatoid arthritis, polymyositis, or systemic lupus erythematosus. Although this classification may be helpful, none of the proposed classes adequately capture the variety of scleroderma clinical presentations [2].

The feature of systemic sclerosis (also known as scleroderma), a condition with an unclear Etiology is skin induration. Systemic sclerosis was often thought to be a dull fibrotic process, but there is now strong evidence that the pathophysiology of the disease involves an active inflammatory process. Additionally, the majority of individuals have immunological abnormalities and micro vascular illness. Although the precise relationship between the immunological and micro vascular alterations and the fibroblast's excess production of collagen and other matrix components is still unknown, new research indicates that immune response products may have direct effects on fibroblasts and endothelial cells in vitro. Recent developments in our knowledge of various clinical features of systemic sclerosis will be the main focus of this study [3]. In spite of differences in case ascertainment methodology and geographic variations in these data, the findings of studies on the prevalence and incidence of scleroderma are contradictory. According to the data that is currently available, the prevalence ranges from 50 to 300 cases per million people, whereas the incidence ranges from 2.3 to 22.8 cases per million people annually [4]. Scleroderma is currently thought to be a complicated polygenic illness that affects genetically predisposed people who have been exposed to particular environmental conditions and/or other stochastic events. There is on going research into the characteristics of these genetic variables and their interactions with environmental influences. The evidence for a strong hereditary connection to scleroderma is discussed in this article. These investigations point to possible pathogenic pathways underlying scleroderma, which could have practical applications in determining disease risk, diagnosis, prognosis, and developing new treatments [5]. Scleroderma patients' histologic features and clinical signs. In Panel A, a patient with limited cutaneous scleroderma in an Oedematous phase demonstrates hyperkeratosis of the nail folds. In a patient with minimal cutaneous scleroderma, fingertip ulceration is seen in Panel B. Panel C shows a lymph histolytic infiltration surrounding vessels of blood in a haematoxylin and eosin-stained skin tissue. Collagenous matrix is heavily deposited across the dermis and extends into the subcutaneous fat layer (haematoxylin and eosin) in Panel D, a skin biopsy specimen from a patient with early widespread illness. Panel E displays medial and intimal thickening in two actuate arteries (asterisks) and one inter lo bar artery (arrow) in the kidney of a scleroderma patient. The tubular epithelium is atrophic, and the glomerular tuft is mostly collapsed. The illness of fibrosis [6].

## 2. EPIDEMIOLOGY

Depending on the geographic area of investigation, the methods used to determine cases, and the observation period, published estimates of the prevalence and incidence of systemic sclerosis (SSc, scleroderma) vary greatly. Incidence rates in the nation's capital have been reported to range from 2.7 cases per million annually during 1947-1968 to 18.7 cases per million annually during 1972-1982. Prevalence estimates in the United States have also fluctuated, ranging from 138 cases per million during 1950-1979 to 286 cases per million in 1985. These disparities could be the result of methodology variations or they could represent actual heterogeneity in the incidence of cases among various populations [7].

Systemic sclerosis is uncommon, which results in limited epidemiological data. Geographical location, case definition, and ascertainment techniques all affect reported incidence and prevalence rates. Globally, incidence rates range from 8 to 56 new cases per million people per year, whereas prevalence rates range from 38 to 341 cases per million people. According to a U.S. study, the prevalence in the Detroit region was 242 cases per million adults between 1989 and 1991, while the

projected incidence was 19.3 new cases per million adults yearly. In 2003, a separate Quebec research discovered that there were 443 instances for every million adults. It's interesting to note that prevalence rates are higher in the US and Australia than in Europe and Asia (Japan and Taiwan, in particular) [8].

## 3. ETIOLOGY

Though the exact cause of systemic sclerosis is not known, it is widely believed that both hereditary and environmental factors play a role in its development.

**a. Factors Related to Genetics**

Systemic sclerosis are linked to clusters of several other autoimmune disorders within families and shows family clustering. Similar to other auto immune disorders including systemic lupus erythematosus, and rheumatoid arthritis, systemic sclerosis has been linked to the huge histocompatibility complex genetic area, according to genome wide association studies. It has been widely accepted that certain human leukocyte antigens (HLA), such as HLA DRB1*1104, DQA1*0501, and DQB1*0301, are linked to systemic sclerosis. Furthermore, the genesis of systemic sclerosis has also been linked to non-HLA loci such PTPN22, NLRP1, STAT4, and IRF5 [9].

**b. Environmental Issues**

Systemic sclerosis is linked to a number of environmental triggers, including infectious agents including parvovirus B19, Epstein-Barr virus, and Cytomegalovirus (CMV). Systemic sclerosis is also linked to silica dust exposure, as well as sporadic exposure to other substances such organic solvents, toluene, xylene, trichloroethylene, and polyvinyl chloride. Notably, there is no evidence linking smoking cigarettes to an increased risk of developing systemic sclerosis. Environmental exposures like contaminated rapeseed cooking oil, which causes toxic oil syndrome, and L-tryptophan, which causes eosinophilia-myalgia syndrome, are linked to a number of scleroderma-like disorders that can be differentiating from systemic sclerosis based on clinical, histo pathological, and laboratory features. Furthermore, several drugs, such cocaine and bleomycin, have been related to the growth of illnesses that resemble systemic sclerosis [10].

## 4. DIAGNOSIS

For the majority of part, systemic sclerosis is determined clinically. When making a differential diagnosis, it is important to take into account a number of different illnesses that can resemble systemic sclerosis. Fasciitis with Eosinophils The hallmark of eosinophilic fasciitis is eosinophilic inflammation of the deep fascia, which causes the upper and lower extremities—aside from the hands and feet—to thicken and develop a woody induration. Eosinophilic fasciitis is not linked to Raynaud phenomenon, and nail fold capillary testing usually shows normal results. In most cases of eosinophilic fasciitis, antinuclear antibodies and some autoantibodies are negative. Contractures that resemble those seen in systemic sclerosis may develop in patients. Underlying cancers may be linked to eosinophilic fasciitis. Eosinophilic infiltrates in the deep fascia are frequently seen histologically in skin biopsies [11].

**I. Scleromyxedema**

Scleromyxedema is typified by papular waxy lesions on the face, neck, fingers, and limbs and usually happens in patients with multiple myeloma or monoclonal gammopathy. Additionally, patients may have related symptoms like dementia and seizures. Scleromyxedema is not similar to the Raynaud syndrome, and nail fold capillary testing usually shows normal results. In cases of scleromyxedema, antinuclear antibodies and certain autoantibodies are usually negative. In terms of histology, a skin biopsy of scleromyxedema frequently shows dermal fibrosis as well as perivascular inflammation and the accumulation of fibrocytes and mucus, which are not usual symptoms of systemic sclerosis [12].

**II. Sclerodema**

Conditions such as diabetes mellitus, monoclonal gammopathy, exhaustion, infections, and cancers can all be linked to sclerodema. The skin on the face, back, and neck appears doughy and indurated in this condition; the digits are usually undamaged. Sclerodema is not linked to Raynaud phenomenon, and the nail fold capillary test seems to be normal. In most cases of sclerodema, antinuclear antibodies and some autoantibodies are negative. Histologically, a skin biopsy of sclerodema often exhibits mucin deposition and dermal fibrosis without perivascular inflammation. 12 a classical manifestation of scleroderma hand is shown in the Figure 1.

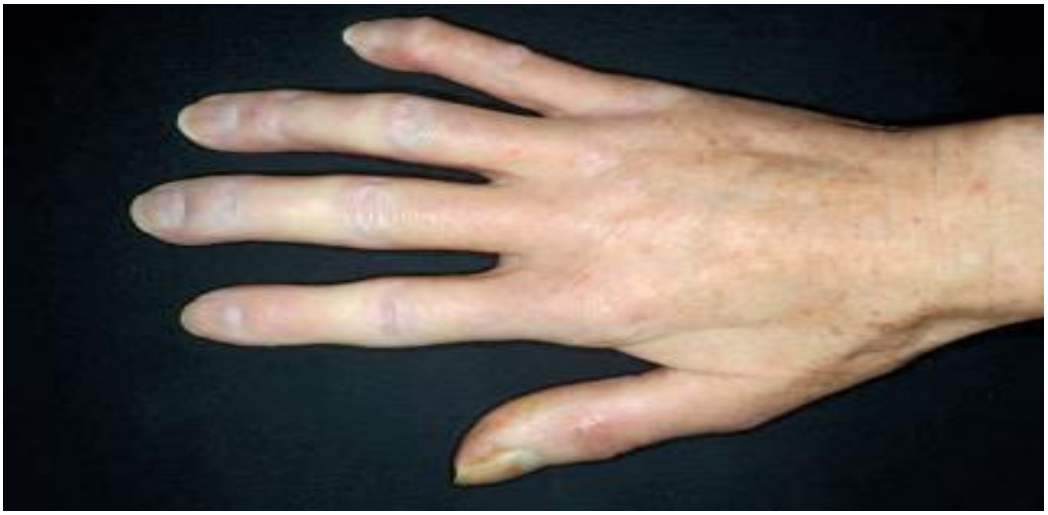

**Figure 1: Clinical feature of Scleroderma in hand [19]**

**III. Systemic Nephrogenic Fibrosis**

Upon being exposed to gadolinium contrast, patients with end-stage kidney failure may have a rare disease known as nephrogenic systemic fibrosis. The hands, feet, trunk, and extremities all have nodular plaques that resemble stone cobblestones but the face is unaffected. Nephrogenic systemic fibrosis is not linked to Raynaud phenomenon, and the nail fold capillary test usually shows no abnormalities. In cases of nephrogenic systemic fibrosis, antinuclear antibodies and certain autoantibodies are usually negative. Histologically, a skin biopsy of nephrogenic systemic fibrosis often exhibits fibrocyte and mucus deposition together with dermal and epidermal fibrosis without perivascular inflammation. 13 a classical Systemic Nephrogenic Fibrosis is shown in the Figure 2.

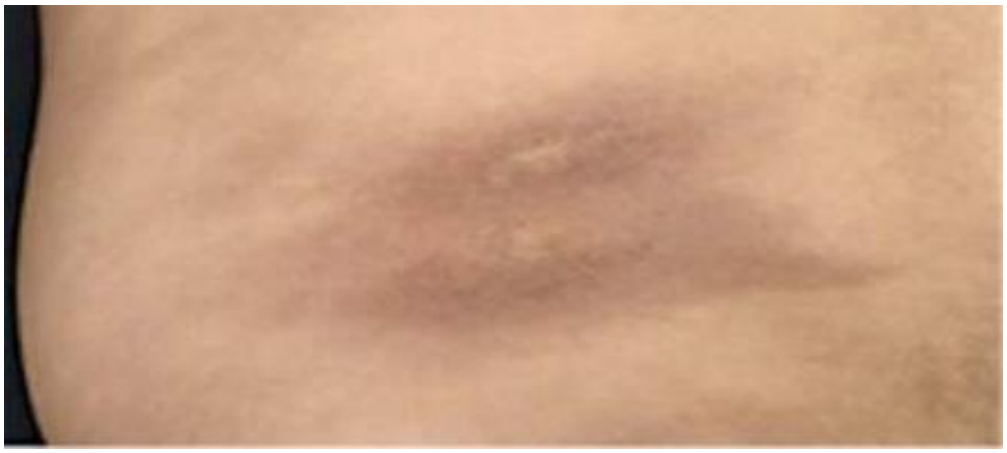

**Figure 2: Systemic Nephrogenic Fibrosis [20]**

**IV. Eosinophilia the Myalgia Syndrome**

L-tryptophan use was linked to this epidemic of symptoms, which included severe myalgias, visceral involvement, and raised CK numbers [13].

**V. Scleroderma localis (morphea)**

One unusual condition is localized scleroderma. Actually, there are 2.7 incidents of morphea and its associated subcategories for per 100,000 people. The estimated prevalence of morphea, in particular, is 50 per 100,000 before the age of 18 and 220 per 100,000 by the age of 80.

Orphea is unusual in people between the ages of 20 and 50 and typically takes place in school-age children. The group with the linear form is 18 years old, but the mean age upon diagnosis is 30 years old. With the exception of the linear subtype, where there is no sex predominance, the male to female ratio is 2.6:1.7. The most common type is plaque-like morphea, which appears as an elevated or depressed brownish or yellow. It represents the Scleroderma localis in the Figure 3.

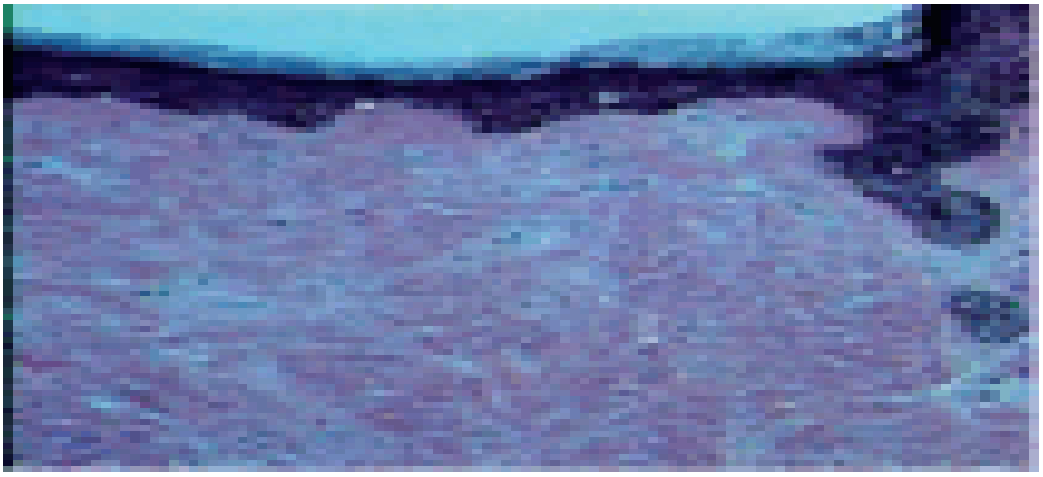

**Figure 3: Scleroderma localis (morphea) [18]**

Atrophy, involving hair and sebaceous gland loss as well as hyper- or hypopigmentation, appears as skin infiltration takes place. Linear bands of sclerosis that can spread to the dermis, subcutis, muscle, and bones and result in deficiencies are the hallmark of linear scleroderma. It is the most frequent kind among kids and teenagers, primarily affecting the trunk and limbs, especially for school-age girls. The linear morphea "en coup de sabre" is an odd variation. Similar to atrophoderma, superficial morphea is a freshly identified variation that affects males and is characterized by minor induration of the hyper pigmented or hypo pigmented patches. A rare and crippling young disease called disabling pansclerotic morphea is marked by quick growth of a deep cutaneous fibrosis that affects the fascia, muscles, and bone, along with contractures and musculoskeletal atrophy. Eosinophilic fasciitis, also known as Schulman Syndrome, is a kind of scleroderma in which symmetrical hardening limbs appear suddenly, sometimes after heavy physical activity.

A unique clinical signal is the "groove" sign, which is the medial upper arm dimpled with elevation, leaving an indentation on the skin above [14].

## 5. PATHOGENESIS

It is unknown what causes systemic scleroderma and localized scleroderma (morphea). Morphoea may be linked to a genetic background as well as extrinsic triggers which involves bacterial (Borrelia Burgdoferi) and viral (BV, varicella) infections, local trauma, surgery, and vaccinations (BCG). Systemic scleroderma may be brought on by environmental triggers like vinyl chloride, silica, certain hydrocarbons, epoxy resins, and rapeseed oil medications, or by infectious agents like bacteria (helicobacter pylori), viruses (CV, BV, and parvovirus B19), or medicines like bleomicin, tryptophan, and appetite suppressants. Specific alleles in the genes for angiotensin converting enzyme (C), tumor necrosis factor, allograft inflammatory protein-1 (F1), monocyte chemo attractant protein-1 (MCP-1), and transforming growth factor-β (TGF-β) have been linked to the suspected disease. There have been observations regarding distinct HLA allele connections with specific autoantibody responses or with disease in various ethnic groups. Another suggested pathogenetic mechanism is micro chimerism. A prolonged allotypic lymphocyte survival in circulating blood, such as fetal cells obtained during pregnancy or cells obtained during transfusion or liver transplantation, is known as microchimerism. Fetal micro chimeric cells have been reported in cell infiltrates of scleroderma lesions and are more prevalent in patients with CSS. Despite having distinct clinical features, morphea and systemic scleroderma have overlaps in that they both cause vascular injury, autoimmunity/immune activation, and excessive collagen deposition.16 a further significant stage in the physiology of both morphea and systemic scleroderma is immune system activation. The majority of mononuclear cell skin infiltrates are caused by CD4+ T-lymphocytes, which release growth factors like transforming growth factor beta (TGF-β) and interleukins like IL-2, profibrotic IL-4, IL-6, and the IL-2 receptor. These factors start and/or keep up the process of fibrosis and vascular injury. Apart from the activation of -lymphocytes, a number of lines of evidence suggest B-cells may also be pathogenic in systemic scleroderma. These include: 1) the overexpression of genes associated with B lymphocytes in scleroderma patients' skin; 2) hyper gammaglobulinemia; 3) self-antibody production; 4) overexpression of C19 on scleroderma B-cells; and 5) a significant association between specific autoantibodies specific to scleroderma and disease subtypes [15].

## 6. TREATMENT

The disease's normal progression cannot be changed by a conclusive treatment or generally accepted disease-modifying substance. Nonetheless, controlling the impacted system or systems has worked well. For better results, early diagnosis is essential. The effectiveness of treatment depends on clinical assessment, organ identification, and disease progression. In order to maximize the quality of life for impacted patients and stop more organ damage, treatment objectives must also be comprehensive and customized. Each person with systemic sclerosis should be educated about the disease and encouraged to seek emotional support, keep a healthy diet and lifestyle, and exercise regularly. A general absence of large randomized controlled trials casts doubt on the effectiveness of some medicines that have been studied for various systemic sclerosis symptoms [16]. In an inpatient information, the infusion can be given continuously; in an outpatient setting, it can be given over eight hours. Usually started at 62.5 mg twice daily for 4 weeks, bosentan can be escalated to 125 mg twice a day. Proximal or distal sympathectomy may be considered in cases that are recalcitrant. Although a few small trials have demonstrated the effectiveness of botulinum toxin injections, their overall efficacy is still limited. Patients who cannot tolerate vasodilator therapy may be treated with vasodilator pumps. In order to properly treat individuals with digital ulcers, wound care is crucial. Skin disease: MTX, HCQ, mycophenolate mofetil, and cyclophosphamide are among the immunosuppressive medications used to treat sclerodactyly. A dose of 15–25 mg of MTX is often given orally or subcutaneously. When prescribed, systemic glucocorticoids are often started at the same time as MTX. The suggested therapy program calls for either oral prednisone at a dosage of 1 mg/kg/d or intravenous (IV) methylprednisolone at a dosage of 30 mg/kg/d for three days in a row each month. MTX is commonly employed to treat patients for one to two years. Gradual weaning of the MTX dose (reduction by 2.5 mg every 2 to 4 weeks) is usually started after 6 to 12 months of verified inactivity. Relapses, however, may occur after therapy stops [17] overall drugs which are used in the management of scleroderma are depicted in the below Table 1.

**Table 1: Management of Scleroderma**

| DRUG | MOA | ROUTE | DOSE | SIDE EFFECT |
|---|---|---|---|---|
| Alefacept | Monoclonal antibody that links to the CD2 sequence of human leukocyte function antigen-3 and stops activation of T cells. | IM, IV | 7.5mg IV<br>15mg IM | Sore throat<br>Cough<br>Itching<br>Chills |
| Azathioprine | Purine analogue that develops form mercaptopurine that inhibits lymphocyte proliferation | PO \ IV | 1 mg \ KG \ DAY | Headache<br>Diarrhoea<br>Vomiting |
| Cyclo phosphamide | Nitrogen mustard leads DNA base pairs to cross-link, damaging them and causing cells that produce blood to die in apoptosis. | PO \ IV | 40 – 50 mg \ kg | Loss of Appetite<br>Nausea, vomiting |
| Mycophenolate | Ionise monophosphate dehydrogenase inhibitor, which leads lymphocytes to generate less the purines. | PO \ IV | 500 mg po<br>1.5 gm iv | Fatigue<br>Dizziness<br>Itching |
| Rituximab | monoclonal antibody targeted against B the cells' expression of the CD20 | IV | 1000 mg iv | Diarrhoea<br>Joint pain<br>Mouth sore |
| Immunoglobulin | Immunoglobulin modulates the immune system. | IV | 2 gms \ kg iv | Nausea, vomiting<br>Rashes<br>Muscle pain |
| Sirolimus | mTOR inhibitor, thereby reducing cytokine-induced lymphocyte proliferation. | PO | 1 mg po | Headache<br>Bone pain |
| Dasatinib | inhibitor of tyrosine kinase that affects many kinds of proangiogenic growth factors, including PDGF and VEGF | PO | 100 mg \day po | Skin rashes<br>Diarrhoea |

## 7. CONCLUSION

"Scleroderma variants" or "scleroderma like disorders" are the phrases used for describing them. A variety of "scleroderma variants"—such as eosinophilic fasciitis, nephrogenic systemic fibrosis, scleromyxedema, and scleroderma. There are still certain aspects of the pathophysiology of scleroderma that need to be clarified. Based on translation targeting, the disease's systemic signature is the same in both infected and not-affected areas. TGF-β, Ras, and reactive oxygen species may all induce various kinds of genes, and it has been established that there is an amplification loop joining the tyrosine kinase receptors (Ras, ROS,

and ERK1/2) with TGF-β and CTGF receptors. Fibroblasts are activated by this circuits.81, 90 Tyrosine kinase inhibitors like PDGFR, serine-threonine kinase inhibitors like TGF-β receptors, and farnesyl tranferase inhibitors like Ras can interfere with the disease process by inhibiting specific signalling pathways.

**Conflict of Interest:** None of the authors have conflict of interest including finance.

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