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Updated Treatment Modalities of Systemic Sclerosis: Review Article

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ABSTRACT

Background: The three defining characteristics of systemic sclerosis (SSc), a chronic connective tissue condition, are fibrosis of the internal organs, joints as well skin, autoimmunity, and vasculopathy. New therapeutic targets are urgently required because there is currently no medication that alters the fibrosis components. This review looks at the state of therapies now and new medicines.

Objective: This review article aimed to assessment of updated treatment modalities of systemic sclerosis.

Methods: We searched PubMed, Google Scholar, and Science Direct for information on Systemic Sclerosis with its treatment. However, only the most current or comprehensive studies from April 2007 to May 2021 were considered. The authors also assessed references from pertinent literature. Documents in languages other than English have been disregarded since there aren't enough resources for translation. Unpublished manuscripts, oral presentations, conference abstracts, and dissertations were examples of papers that weren't considered to be serious scientific research.

Conclusion: The development of progressive pharmacological therapy strategies in conjunction with non-pharmacological procedures is the foundation for the treatment of SSc and is established on the regular and routine examination of any possible organ injury. Based on unique traits of the patient and the SSc, several advancements have been accomplished, particularly in the fields of targeted treatments and customized medicine.

Keywords: Systemic sclerosis, Pharmacological therapy strategies, Quality of life.

INTRODUCTION

A chronic connective tissue illness called systemic sclerosis (SSc) is distinguished by fibrosis of joints and skin as well as internal organs, blood vessels as well as autoimmune impact. It has a higher mortality rate than would be predicted from the general population and when compared to some of the other rheumatic diseases [(1)].

The multisystem condition SSc is rare, clinically diverse, and has a significant impact on the physical and psychological functioning of patients as well as their capacity to engage in social and occupational activities. To reduce symptoms and impairment, as well as to enhance functional capacity and health-related quality of life (QoL), is one of the most difficult aims of treatment [(1)].

Inflammation, fibrosis, and vasculopathy all share a number of pathogenic pathways with systemic sclerosis (SSc), a complicated rheumatologic autoimmune disease that causes damage to internal organs. Now that the disease's pathophysiology has been clarified, and new therapeutic targets have been found. Many of these targets have been tested in preclinical and clinical trials with varying degrees of success. New therapeutic targets have also been found as a result of recent research on the participation and interplay of the innate and acquired immune systems [(2)].

Clinical Manifestation:

Diffuse cutaneous systemic sclerosis (dcSSc) and restricted cutaneous systemic sclerosis (lcSSc) are the two primary subtypes of systemic sclerosis, and they differ in the location of skin involvement. Calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasis, or CREST syndrome, is the previous term for restricted cutaneous systemic sclerosis [(3)].

Both systemic sclerosis and morphea (localized scleroderma) are frequently referred to under the umbrella term "scleroderma" (systemic scleroderma). It's crucial to distinguish between the two since they have extremely distinct symptoms and treatment requirements [(3)].

The key features of systemic sclerosis are:

Sclerodactyly, the thickening of the skin of the fingers and toes blood levels of certain autoantibodies (such as anti-Scl70 or anti-centromere antibodies), abnormal capillaries in the nail fold (Figure 1), Internal organ fibrosis as well as vascular damage affecting the kidneys, heart, lungs, and/or digestive system [(3)].

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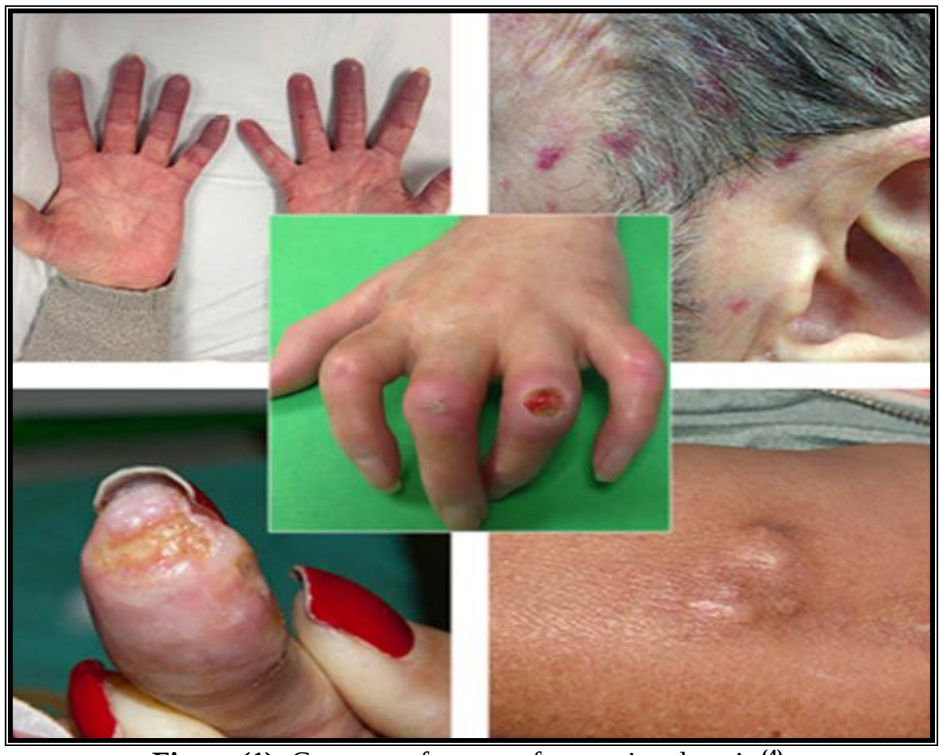

Figure (1): Cutaneous features of systemic sclerosis [4].

TREATMENT

Treatment of cutaneous disease associated with SSc:

Recent therapy in treatment of cutaneous manifestations:

- **Abatacept:**

The human fusion protein abatacept blocks the activity of the CD80-CD86 molecule, which is involved in co-stimulatory signaling. This barrier limits the secretion of certain cytokines by T cells by preventing them from activating their antigen-presenting cells. There have been a lot of basic observational studies showing that activated T cells and their cytokines play a role in the development of systemic sclerosis [3-7].

- **Rituximab:**

The biologic with the most systemic sclerosis studies has been rituximab. The CD20-antigen on B cells is recognized by the monoclonal chimeric human-mouse antibody rituximab, which then kills cells by interfering with the Fc region. Preclinical investigations have supported the idea that rituximab may be useful in treating systemic sclerosis since it seems that B lymphocytes play a pathogenic role in this condition [8].

- **Tocilizumab:**

The IL-6 receptor is the target of the humanized recombinant monoclonal antibody tocilizumab. Since IL-6 has been demonstrated to directly promote fibrosis, it is believed to be the root cause of systemic sclerosis [7].

Hematopoietic stem cell transplantation (HSCT):

Despite its potential as the most effective disease-modifying therapy for carefully chosen patients with early dcSSc, HSCT has the greatest treatment-related mortality of any approach now used to treat the illness. It seems that the selection of patients, the mobilization and conditioning approach, and the local competence of the transplant facility are the most critical aspects [8].

Raynaud's phenomenon as well as digital ulcers (DU) management:

Non pharmacological treatment:

The excruciating pain associated with DU can linger for months or even years depending on how aggressive the DU is. Despite being often administered, since nonsteroidal anti-inflammatory drugs (NSAIDs) increase the risk of kidney damage and gastrointestinal sickness, they should be substituted with acetaminophen or opiates instead [9].

Pharmacological treatment:

Dihydropyridine-type calcium antagonist:

The most current guidelines for treating systemic sclerosis from the European League Against Rheumatism (EULAR) state that oral nifedipine and nicardipine should be used as first-line treatment for Raynaud's phenomenon (RP). Taking these drugs may reduce the likelihood of developing an ulcer [10].

- **Prostacyclin analogues:**

Individuals with severe digital ulcers (DU) and digital vasculopathy due to SSc are candidates for treatment with iloprost. Furthermore, it is the recommended therapeutic option for DU as a primary therapy [11].

Oral endothelin receptor blockers

When calcium antagonists have failed to treat numerous digital ulcers in patients with diffuse systemic sclerosis, new EULAR guidelines suggest using bosentan. Patients

with SSc, and especially those with DUs, have elevated serum endothelin-1, which serves as a biomarker of vascular severity in a manner similar to that seen in patients with pulmonary hypertension [12].

- **Nitrates:**

Topical, sublingual, or oral formulations used in combination with other medications for RP and DUs have not been the subject of any published randomized, controlled research examining the influence on DUs healing [13].

- **Phosphodiesterase inhibitors:**

Patients experiencing RP episodes have been proven to benefit from sildenafil, although its effects on DUs are less well understood [13].

- **Statin:**

Treatment with oral atorvastatin at a dosage of 40 mg daily dramatically decreased endothelial dysfunction in SSc patients as a result of its anti-inflammatory and immunomodulatory properties. Additionally, studies showed that after taking atorvastatin, as opposed to the placebo group, nitric oxide levels increased and endothelin-1 levels decreased [13].

Ultraviolet-A (UVA-1) phototherapy:

It is significant that a thorough investigation of UVA-1's effects on involvement of skin among SSc who had with early inflammatory responses and beyond, the hands has not been conducted. Various retrospective analyses suggest that this patient group may benefit from UVA-1 phototherapy.

The ideal UVA doses and techniques are currently being explored since it is unclear how long UVA-1 phototherapy should persist for specific SSc subgroups. However, if systemic immunosuppressives are contraindicated, medical professionals who explored UVA-1 phototherapy to be considered as adjuvant therapy as either an adjunct or first line treatment for individuals with early diffuse cutaneous manifestations [14].

Treatment of SSc-related interstitial lung disease:
Symptomatic treatments:
Immunosuppresive drugs:

- **Mycophenolate Mofetil (MMF):**

People at risk for progressive interstitial lung disease (ILD) due to SSc often start on mycophenolate mofetil (MMF), a lymphocyte proliferation inhibitor. In the Scleroderma Lung Study II, the efficacy of MMF in SSc-ILD was evaluated in 142 patients having a pulmonary function test (PFT) of less than 80% and HRCT findings of ground glass opacities. Treatment options for the participants were 1,500 mg MMF twice daily for 24 months and oral cyclophosphamide (CYC) titrated up to a maximum dose of 1.8-2.3 mg/kg for 12 months. Lower rates of leukopenia and thrombocytopenia were seen with MMF compared to cyclophosphamide (CYC), and the drug was generally well tolerated [15].

- **Cyclophosphamide (CYC):**

The results of the Scleroderma Lung Study II indicate that cyclophosphamide (CYC) might be an alternative to MMF. In addition to the six CYC infusions that must be given each month, a complete blood count, kidney function, and urinalysis should be performed every single month. With CYC, corticosteroid pulses have been successfully employed, but not as the exclusive form of treatment. Typically, after a period of CYC, the medication is changed to a maintenance medication with less side effects, such as MMF or azathioprine [13].

- **Azathioprine:**

Although they haven't been explicitly compared, azathioprine and cyclophosphamide seem to be less effective as the first line of treatment for SSc-ILD than MMF [16].

- **Bosentan:**

Pulmonary hypertension is managed with bosentan, a non-selective endothelin receptor antagonist. The endothelin system is known to have a role in the pathogenesis of SSc and may be able to slow the course of SSc-ILD [12].

Biological Immunotherapies:

- **Rituximab:** For patients with refractory SSC-ILD treatment is advised [16].
- **TociIizumab:** In individuals with mild ILD, higher blood IL-6 concentrations in those with SSc-ILD seem to be a marker for early disease progression, this might be used to target therapy for this patient group [17].
- **Bortezomib:** The FDA has authorised the drug bortezomib for the treatment of multiple myeloma. Bortezomib promotes healthy repair, suppresses TGF- signaling in vitro, and prevents lung fibrosis [16].

Anti-fibrotic Agents:

Due to their anti-fibrotic actions, nintedanib and pirfenidone have been licensed for the treatment of people with idiopathic pulmonary fibrosis (IPF). Pirfenidone (1,200-1,800 mg/day) was related with a reduction in dyspnea and an increase in VC in a case study involving 5 persons with SSc-ILD (by 10 percent from baseline). Treatment with the tyrosine kinase inhibitor nintedanib for patients with idiopathic pulmonary fibrosis has been shown to increase survival and decrease the length of time they have to be sick. This is because nintedanib blocks the action of CSF1R, fibroblast growth factor, platelet-derived growth factor, and vascular endothelial growth factor (VEGF) IPF [18].

Treatment of pulmonary arterial hypertension associated with SSc (PAH-SSc):

Prostaglandins:

Patients with PAH who used the drug epoprostenol (prostacyclin) had improvements in their exercise tolerance, cardiopulmonary hemodynamics, functional class (as determined by the New York Heart Association), and symptoms. Randomized clinical studies have shown that epoprostenol, the first drug designed particularly for PAH, significantly improves survival [(19)].

Based on a recent clinical trial that employed the amount of time between the start of therapy and the first incidence of a composite endpoint as a main endpoint, the FDA recently authorized the new dual endothelin receptor antagonist macitentan for the treatment of PAH [(20)].

Riociguat, a brand-new medication newly authorised by the FDA, stimulates soluble guanylate cyclase (sGC), a crucial enzyme in the signaling route for nitric oxide. As a result, riociguat is the first medication in a brand-new family of sGC stimulators used to treat PAH [(21)].

Treatment of GIT disease associated with SSc:

Non-pharmacological treatment:

Three points were used to condense the most recent therapy management into the most recent update of EULAR guidelines, which was released in 2017:

Treatments for symptomatic SIBO include prokinetics for regulation of GIT dysmotility, proton pump inhibitors (PPI) for GERD due to SSc and prevention of esophageal strictures, ulcers, and other complications, and intermittent or cyclical antibiotic administration [(22)].

Cannabinoid, muscarinic, opioid, and other new pharmaceutical targets being researched include nitrous oxide synthase to lessen transitory LES relaxation [(22)].

Prospects for future treatments, novel treatment options for SSc-GIT involvement are being researched, especially immunosuppressive medications that target intravenous immunoglobulin (IVIG) and pro-fibrotic cytokines. Multiple effects of IVIG treatment include the decrease of pro-fibrotic cytokines and anti-idiotypic-mediated neutralization of circulating muscarinic, anti-fibroblast, or anti-endothelial cell autoantibodies. Compared to immunosuppressive medications, IVIG has a superior safety record [(23)].

Treatment of renal disease associated with SSc:

ACE inhibitors (ACEI):

An ACEI should be started as soon as SRC is diagnosed, or the dose should be raised if the patient is currently taking one. There is no proof that a once-daily medicine is always superior to a short-acting ACE inhibitor (such captopril), however it may be in the case of a hemodynamically unstable patient. Any increase in serum creatinine following an increase in ACEI dosage shouldn't result in dose decrease or stopping ACEI therapy [(24)].

Other antihypertensives:

According to the available data, ACEI are more effective in treating SRC than ARBs. If blood pressure is still too high after ACEI and ARB combination therapy, further antihypertensives, such as calcium channel blockers, doxazosin, and clonidine, may be added to the treatment regimen [(24)].

CONCLUSION

Internal organ and cutaneous fibrosis may occur as a result of the connective tissue condition systemic sclerosis. Scleroderma treatment is still difficult because there aren't any specific medicines available. Despite methotrexate's continued dominance, research evaluating the efficacy of alternative medicines such MMF, IVIG, and UVA-1 phototherapy are encouraging for the treatment of scleroderma-related cutaneous illness. One's specific organ problems should be taken into account while choosing and managing medications for scleroderma treatment.

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