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Systemic Sclerosis—A systematic review on therapeutic management from 2011–2014

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Abstract

Purpose of review—To review pharmacologic and non-pharmacologic therapies in the treatment of systemic sclerosis (SSc) from 2011 to 2014 through a systematic review.

Recent Findings—Our systematic review identifies randomized controlled trials (RCT), meta-analyses, systematic reviews, case series and observational studies which support organ based therapy with known immunosuppressive agents, novel agents, and hematopoietic stem cell transplantation (HSCT), and also includes non-pharmacologic therapies improving visceral and physical function.

Summary—SSc is an orphan autoimmune disorder with significant morbidity and mortality. Although there has been significant progress over the years in therapeutic options for SSc, the mainstays of treatment are organ based and primarily symptom management. Our systematic review of the last 4 years of treatment emphasizes known treatment strategies already in practice, but also identifies new therapeutic approaches with additional biologic agents and HSCT.

Keywords

systemic sclerosis; treatment; pharmacological; non-pharmacological

Introduction

Systemic sclerosis (SSc) is an autoimmune disorder that encompasses inflammation, vascular and fibrotic processes, which affect multiple organ systems including the heart, lungs, kidneys, gastrointestinal (GI) tract, blood vessels and skin. Although there has been significant progress over the years in development of therapeutic options for SSc, the mainstays of treatment are organ based and primarily for improvement in symptoms.

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Conflicts of interest:

Dr. Khanna has/had consultancy relationship with Bayer, Biogen Idec, Bristol Myers Squibb, Cytos, EMD Serono, Genentech/ Roche, Gilead, Glaxo SmithKline, InterMune, Lycera, Medac, Sanofi-Aventis/Genzyme, and Seattle Genetics and has received research funding from Scleroderma Foundation and Pulmonary Hypertension Association.

We performed a systematic review of pharmacological and non-pharmacological interventions for the treatment of SSc from 2011 through 2014. With the assistance of our expert librarian (WT), we searched PubMed, EMBASE, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) to find all articles from January 2011 through December 2014 on pharmacological and non-pharmacological therapy of SSc. A broad search strategy was conducted with various concept clusters and terms related to SSc and various pharmacological and non-pharmacological treatment terms, which resulted in a total of 2,407 citations retrieved. The titles and abstracts were reviewed for relevance by the mention of SSc and/or scleroderma and treatment. If the title and/or abstract indicated a review article for connective tissue disease or autoimmune disease, the manuscript was searched for the terms “systemic sclerosis” and/or “scleroderma” and “treatment” and if it did not meet those criteria, it was excluded. Also, if the article met one of the following exclusion criteria, it was excluded: not written in English, no human subjects, or a case series of less than 20 SSc patients. Four-hundred and seventy-four articles satisfied the inclusion criteria. Those 474 articles were reviewed and articles were excluded if they were not an original study such as a case series, systematic review, meta-analysis, or randomized controlled trial (RCT). This resulted in 72 articles, and of those 72 articles, 28 were excluded for the following: it was an abstract without a publication, did not focus on clinical outcomes, focused on adverse events of an agent, focused on the pharmacology of the medication, or it focused only on the variability in use of the intervention instead of the outcome. This resulted in 44 manuscripts for systematic review based on organ system and therapeutic management.

Skin

Skin involvement of SSc is almost universal. Therapy typically focuses on more aggressive forms of skin disease, such as early diffuse cutaneous SSc (dcSSc) [1*]. There are various treatments available including immunosuppressive agents, novel agents, and non-pharmacological therapy.

A small pilot study assessed use of hyperimmune caprine serum (AIMSPRO, Anti-inflammatory IMMuno – Suppressive PROduct), which is a goat serum extract derivative that contains items such as caprine immunoglobulin and cytokines. It has an unclear mechanism of action, but has an immunomodulatory role and studies in multiple sclerosis and chronic inflammatory demyelinating polyneuropathy have shown an effect on sodium channels. AIMSPRO was tested in a RCT of 20 patients with dcSSc with disease duration greater than 3 years. There was a trend towards skin improvement and no safety concerns were evident [2].

Intravenous immunoglobulin (IVIG) is another potential agent for skin involvement. IVIG has immunomodulatory and anti-inflammatory effects in autoimmune disorders. Its specific mechanism of action in SSc is unknown, although it has had an anti-fibrotic effect in animal models, and it has been reported to be effective in treatment of other fibrotic conditions such as scleromyxedema [3]. In a multicenter RCT in Japan, 63 dcSSc patients were treated with a single course of IVIG versus placebo. There was not a significant difference between treatment and placebo groups; however, in those patients who received additional IVIG

courses due to lack of response in the double-blind portion of the study, there was improvement in modified Rodnan skin score (MRSS), a validated measure for skin thickness used as a key outcome measure in clinical trials [4, 5]. Also, in a single center retrospective study, 30 patients with active refractory dcSSc received six, monthly courses of IVIG, (with or without immunosuppressive therapies), resulting in statistically significant improvement in MRSS along with improvement in reported outcomes [6].

The use of tyrosine-kinase inhibitors, such as imatinib, a potent inhibitor of platelet-derived growth factor and transforming growth factor- β pathways, has shown inconclusive effects on outcomes and frequent intolerance. A phase II RCT involving 25 patients with limited cutaneous (lcSSc) and dcSSc evaluated the effects of imatinib 400mg daily versus placebo on skin fibrosis. This study did not show a significant response to treatment after 6 months [7]. In a proof-of-concept pilot RCT, 10 patients with active dcSSc were treated with imatinib 200mg BID for 6 months, but due to intolerance and high rates of adverse events in the imatinib group, the study enrollment was stopped. Even with dose reduction, imatinib was still poorly tolerated, and due to its reduced sample size from intolerance, conclusions regarding its efficacy could not be made [8]. Also, in an open label trial of 24 patients with dcSSc treated with imatinib 400mg daily for 12 months, there was improvement in skin thickness at 12 months, but there were many adverse events possibly related to imatinib [9].

Biologics are another area of skin treatment undergoing further study. A systematic review on biologic therapy concluded that the effectiveness of TNF-antagonists on skin fibrosis is uncertain [10]. However, rituximab is showing promise. In an open label clinical trial of 20 progressive dcSSc patients, with and without lung disease, rituximab was associated with improved skin scores in all but 1 patient and was generally well tolerated even with repeated courses, which suggests rituximab may have a role in early dcSSc [11]. However, there was no control group and a double-blind RCT is ongoing. The European Scleroderma Trial and Research (EUSTAR) cohort was used to perform a post-hoc, nested case control, observational study to assess the outcome of treatment with rituximab on skin and lung fibrosis in 63 patients with SSc. In 25 patients with severe dcSSc, the MRSS was significantly improved after approximately 6 months of therapy compared to matched controls [12].

In addition, two case series at scleroderma centers suggested efficacy of mycophenolate mofetil in early dcSSc [13, 14].

Non-pharmacologic management

One type of non-pharmacological therapy is use of extracorporeal shock waves (ESW), which have anti-inflammatory and regenerative effects on various tissues [15]. ESW therapy was evaluated in 29 patients with dcSSc and lcSSc, which reported statistically significant improvement in MRSS immediately after initial treatment and at day 7 and day 30 after treatment compared to baseline and reported statistically significant improvement in visual analog scale (VAS) for skin wellness at all time points up to 90 days compared to baseline [15].

A significant concern of many SSc patients is decreased oral aperture which can lead to psychological stress, decreased function and decreased oral hygiene. In a study to evaluate the effect of adaptive oral hygiene devices and orofacial exercise on gingival health in SSc patients, 48 patients were randomly assigned to receive the intervention including objects such as a powered toothbrush, flosser with a handle and orofacial exercise or be in the control group who used a manual toothbrush with dental floss. There was a significant and larger decrease in gingival inflammation in the intervention group, which supports the use of adaptive devices and orofacial exercise in SSc patients [16]. However, in another 48 patients with SSc, who were randomized to be in an orofacial exercise program or control group, there was not significant improvement at 6 months and the adherence to the exercise program was poor [17].

Summary—There are no conclusive trials to guide management of skin involvement in SSc. However, there are encouraging results of pilot studies, but these studies are open label and inadequately powered. In patients who do not respond to methotrexate or mycophenolate mofetil, IVIG or rituximab may be effective in refractory cases. There are ongoing studies that are double-blinded and adequately powered to assess different biologics in treatment of skin involvement in SSc.

Musculoskeletal

Many patients with SSc have musculoskeletal involvement, such as inflammatory arthritis or myopathy. In a systematic review on biologic therapy for SSc, observational studies suggested improvement in inflammatory arthritis with anti-TNF alpha agents, such as etanercept and infliximab [10]. In a EUSTAR prospective observational study, tocilizumab and abatecept were studied in 20 patients with refractory polyarthritis and 7 patients with refractory myopathy. Both were reported to be effective in refractory polyarthritis but abatecept was not effective in myopathy [18].

Recent data has been emerging regarding non-pharmacologic therapy for hand involvement of SSc patients. In a controlled clinical trial, a self-administered kinesiotherapy regimen at home showed some beneficial effects in hand mobility [19]. An evaluation of self-management using a workbook and DVD in 49 patients with SSc, also suggested improvement in hand function in addition to a decrease in pain, depression, and fatigue [20].

Summary

There are no pharmacological clinical trials for musculoskeletal treatment of SSc, but case series have shown benefit for inflammatory arthritis with use of TNF antagonists, tocilizumab, and abatacept. Ongoing trials with these agents (e.g., abatacept [<http://umich.edu/~asststdy>]) will help provide additional data on efficacy in inflammatory arthritis.

Cardiopulmonary

Treatment of interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) is an important area of discovery as cardiopulmonary involvement is now the leading cause of death in patients with SSc.

Pulmonary arterial hypertension

There are various categories of PAH medications including endothelial receptor antagonists (ERA) (bosentan, macitentan, and ambrisentan), phosphodiesterase-5 (PDE5) inhibitors/soluble guanylate cyclase stimulators (sildenafil, tadalafil, and riociguat) and prostacyclins (iloprost, epoprostenol, and treprostinil) [1*].

In our review, we found 2 articles discussing cohort evaluation of these various medications. Although the aforementioned pharmacologic therapy is approved for PAH, a retrospective cohort of 99 patients in a single center with SSc-related PAH (SSc-PAH) and SSc-related PH-ILD treated with PAH medications suggested that early use of prostanoid therapy, within 6 months of diagnosis, may be associated with improved transplant-free survival in those patients with SSc-related PH-ILD [21].

Despite availability of different agents with complementary mechanisms of action for PAH, a retrospective single center analysis from 1996 to 2010, which includes epoprostenol treatment only prior to 2002 followed by the introduction of ERA and PDE5 inhibitors, found that mortality of patients with SSc-PAH has not improved since epoprostenol has emerged as a therapy. However, other evidence has suggested that early detection can improve outcomes [22].

Another area of controversy is whether there is a survival advantage in SSc-PAH with use of warfarin, despite increased risk of bleeding due to underlying gastric antral vascular ectasia (GAVE) and concomitant comorbidities. In an observational study with 275 patients with SSc-PAH, of whom 78 patients were treated with warfarin, data analysis suggested a low probability of improving survival in SSc-PAH [23].

In a systematic review by Khan et al evaluating the survival of SSc patients treated with lung transplant compared to lung transplant survival in idiopathic pulmonary arterial hypertension (IPAH) and ILD patients, the results suggest that short and intermediate survival after lung transplantation is similar [24].

Summary—There are many FDA approved therapies available for management of SSc-PAH. Overall survival has not substantially improved compared to pre-treatment era, but early screening and diagnosis appear to have a survival benefit in SSc-PAH [25].

Interstitial lung disease

Treatment of SSc-related ILD (SSc-ILD) should be considered in patients who have early progressive ILD with moderate to severe lung involvement with worsening lung function. The most frequently used medications include cyclophosphamide, mycophenolate mofetil and azathioprine. Cyclophosphamide has been previously studied in 2 RCTs, the Scleroderma Lung Study and the Fibrosing Alveolitis in Scleroderma Trial (FAST), both which supported the use of cyclophosphamide for SSc-ILD. In our review, there were case series, cohorts, systematic review and meta-analysis evaluating cyclophosphamide. These suggested stabilization rather than improvement in FVC and DLCO in SSc-ILD [26, 27, 28, 29, 30]. Also, although cyclophosphamide has had the only RCT published to date, in a

recent retrospective cohort, azathioprine was found to have beneficial effects in some patients with ILD [31].

Imatinib has been evaluated in multiple pilot studies, but as stated previously, results have been controversial and the drug has been poorly tolerated. In a phase I/IIa, open label pilot trial, 20 patients with SSc-ILD were treated with imatinib up to 600mg daily, but only 12 patients completed the study and 7 discontinued the study due to adverse events and/or disease progression. The preliminary results on efficacy suggested there could be a favorable effect of imatinib on MRSS and FVC [32]. In a cohort of SSc patients unresponsive to cyclophosphamide for ILD, 30 patients with active pulmonary disease were treated with low dose imatinib at 200mg/day for 6 months. Of the 26 patients who completed the study, approximately 73% had improved or stabilized pulmonary disease at 6 months [33].

Rituximab is also showing promise as a new therapeutic option in various manifestations of SSc, particularly ILD. In a case control study using the EUSTAR cohort, 63 patients with SSc-ILD treated with rituximab were reported to have prevention of worsening lung fibrosis [12]. In an open-label, uncontrolled study, the efficacy of rituximab was evaluated in 20 patients with progressive dcSSc and suggested rituximab preserves pulmonary function [11].

Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) is an emerging treatment option for patients with early progressive SSc. The Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial was a randomized, open-label, parallel group trial performed in 156 patients with early dcSSc (majority (>85%) with ILD) to compare safety and efficacy of autologous HSCT versus 12 months of intravenous pulse cyclophosphamide. This study suggests that patients treated with HSCT had improvement in long term event free survival, overall survival at the median follow up of approximately 6 years, MRSS, FVC% and patient reported outcomes at 2 years. However, within the first year, there were more events, including treatment-related deaths, in the HSCT group than the cyclophosphamide group [34**]. Additional evidence supporting HSCT comes from 2 other studies including an open-label, randomized trial and a retrospective study [35, 36]. SSc patients who are ideal candidates for HSCT may be those non-smokers whose disease did not respond to standard treatment along with either of the following characteristics: dcSSc within the first 4 to 5 years with mild to moderate organ involvement (especially ILD); or limited cutaneous SSc (lcSSc) with progressive visceral involvement [37].

Summary—Data suggest a role of cyclophosphamide as induction therapy in patients with SSc-ILD. In patients who achieve stabilization, consider switching to mycophenolate mofetil or azathioprine (if mycophenolate mofetil is not approved). We await results of the Scleroderma Lung Study II, which compares mycophenolate versus cyclophosphamide in SSc-ILD. In patients who do not respond to cyclophosphamide, there is uncertainty on the next steps. Preliminary data suggest rituximab or imatinib may be effective but the risk/benefit ratio needs to be determined in larger controlled trials. HSCT may be an option for patients who have progressive ILD.

Vascular

Raynaud's phenomenon (RP) is the most common manifestation of SSc and can be complicated by digital ulcers and even digital ischemia, necessitating ongoing development of improved treatment strategy. There have been various pharmacological and non-pharmacological therapies evaluated recently.

In a meta-analysis of double blind, RCTs evaluating RP with PDE5 inhibitor treatment, its use had a significant benefit on Raynaud condition score and the frequency and duration of RP attacks compared to placebo [38**]. A RCT using modified-release sildenafil also supported its use in RP [39].

In a RCT, the effect of udenafil 100mg daily and amlodipine 10mg daily were compared in 29 patients with secondary RP with SSc and other connective tissue diseases. Both agents had similar efficacy with decrease in RP frequency of attacks [40].

A meta-analysis of 31 RCTs comparing the effects of pharmacologic therapy versus placebo in healing or prevention of digital ulcers in SSc patients suggested statistically significant improvement/healing of digital ulcers with PDE5 inhibitors, prevention of new digital ulcers with bosentan in 2 RCTs, and prevention of new digital ulcers with IV iloprost, whereas oral prostacyclins were statistically similar to placebo. Also, a trial for atorvastatin reported a statistically significant benefit in prevention of digital ulcers compared to placebo, and a trial for topical vitamin E reported a statistically significant benefit in healing of digital ulcers compared to placebo [41**].

Botulinum toxin injections have shown statistically significant improvement in hand function and improvement in symptoms such as pain, cold intolerance, color change, and ulceration up to 12 weeks after treatment according to an observational study [42] and is used in clinical practice for resistant cases of RP [1*].

There are various non-pharmacological options for digital ulcers in SSc. In a systematic review, a pilot study of intermittent compression of upper extremity digital ulcers resulted in healing of most ulcers and improved pain [43]. Also, biofeedback and deep oscillation physiotherapy have shown potential [44].

Summary

Meta-analysis suggests the efficacy of PDE5 inhibitors for RP and digital ulcers. Amlodipine at 10 mg daily appears to be effective compared to PDE5 inhibitors. Meta-analysis supports the use of prostacyclin for prevention of digital ulcers and bosentan for prevention of digital ulcers (especially in patients with high ulcer burden).

Renal

Scleroderma renal crisis (SRC) is a feared complication of SSc and was previously the most common cause of death. Those most at risk are patients with early disease, particularly dcSSc, and who also have anti-RNA polymerase III antibodies [1*]. One of the known contributors to SRC is high dose glucocorticoids, and this was confirmed in a retrospective

observational study of 410 patients with SSc [45]. Also, in a systematic review evaluating original prospective clinical studies of SSc patients newly introduced to corticosteroids, 26 studies were included with a total of 500 SSc patients of which there were 10 cases (2%) of SRC, which all received medium dose (16mg to 30mg daily) to high dose (IV pulses or greater than 30mg daily) corticosteroid therapy and 7 cases occurred in those receiving HSCT. In patients with early dcSSc, SRC rate was 4% [46].

Summary

SRC can be associated with corticosteroids, particularly with doses of prednisone equivalents greater than 15mg daily. Steroids can be used if needed in patients with SSc, but should be in doses of less than 15mg daily and should be avoided if possible in those patients with early disease, especially those with dcSSc and who have anti-RNA polymerase III antibodies. However, despite ACE inhibitor use being the treatment of choice in SRC, prophylactic use of ACE inhibitors has not shown improved outcomes, and a recent study suggests increased mortality in patients treated with ACE inhibitors prior to SRC; thus, the prophylactic use of ACE inhibitors is generally not recommended [1*, 47].

Gastrointestinal

GI involvement in SSc is common, affecting up to 90% of patients. In our review, 2 articles met our search criteria for GI treatment. One emerging therapy for treatment of gastroparesis is ghrelin. Ghrelin is a gut hormone that stimulates gastric motility and accelerates post-prandial gastric emptying. In a crossover RCT, 10 patients with SSc with GI involvement received an infusion of either ghrelin or saline. The gastric emptying rate was accelerated with ghrelin, but symptoms of post-prandial satiety did not change. No serious adverse events were reported [48]. In another article, Sallam et al systematically assessed the use of complementary alternative medicine use in SSc. They concluded that various types of acupuncture related therapies may be promising for GI involvement as well as gastric electrical stimulation for refractory gastroparesis and sacral nerve stimulation for fecal incontinence [49].

Summary

Treatment of GI involvement is primarily symptomatic with new studies emerging for treatment ranging from hormonal therapies to complementary alternative medicine therapies.

Conclusion

Advances in the treatment of SSc are needed given its significant morbidity and mortality due to its multi-organ system involvement. There have been various studies on SSc treatment over the last 4 years, many of which are RCTs and meta-analyses, but they often have small study populations due to the rare occurrence of SSc. However, our systematic review provides increased evidence on previously known therapy outcomes, but also provides some evidence of promising therapy alternatives that can be used, but more RCTs are needed, some of which are currently underway.

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Key Points

- Treatment of skin involvement of early dcSSc involves methotrexate or mycophenolate mofetil as initial agents, and biologics have shown benefit in SSc associated inflammatory arthritis in observational cohorts.
- Early screening for SSc-PAH appears to have a survival benefit.
- Cyclophosphamide can be used for induction therapy in progressive SSc-ILD.
- HSCT appears to be a promising therapy in severe, progressive SSc.
- Steroids are associated with SRC and prophylactic ACE inhibitors are not recommended.