Symposium - Pediatric Dermatoses

Scleroderma in children: Emerging management issues

Saumya Panda

Department of Dermatology, KPC Medical College, Kolkata, India

Address for correspondence: Dr. Saumya Panda, 18 D/11, Anupama Housing Complex, Phase I, VIP Road, Kolkata – 700 052, India. E-mail: saumyapan@gmail.com

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ABSTRACT

Scleroderma is a set of rare connective tissue diseases of unknown etiology. It is characterized by thickening and hardening of the skin. Scleroderma is divided into two main subgroups: systemic and localized. The systemic form, also known as systemic sclerosis, involves diffuse skin involvement associated with fibrotic changes in internal organs. Juvenile localized scleroderma is a more common entity and is usually confined to a specific region of the body with no internal organ involvement. Therapeutics are divided into three main subgroups for juvenile systemic sclerosis: antifibrotics, anti-inflammatories, and vasodilators. For localized disease, anti-inflammatories, vitamin D analogues, and UV irradiation have been investigated. The rarity of scleroderma in children and the self-limiting nature of the disease together make randomized controlled trials very difficult. Therefore, most data on therapeutic modalities for this condition have to be extrapolated from studies conducted on adults. International cooperation, following a standardized operation protocol, is needed to validate these and future interventions such as autologous stem cell transplant and cytokine-directed therapies.

Key words: Juvenile localized scleroderma, juvenile systemic sclerosis, scleroderma

INTRODUCTION

Scleroderma is a set of rare and complex connective tissue diseases of unknown etiology. They encompass a range of clinical characteristics that result from excess collagen deposition in tissues leading to fibrosis.[1] Scleroderma is classified into two major subtypes: systemic and localized [Table 1].[2]

JUVENILE SYSTEMIC SCLEROSIS

Juvenile systemic sclerosis (JSSc) is a chronic multisystemic connective tissue disorder characterized by symmetrical thickening and hardening of the skin, associated with fibrous changes in internal organs.[3] Although rare in children, it represents one of the most severe rheumatic conditions in pediatric rheumatology practice.[4] Recently, a Committee on Classification Criteria for JSSc, including members of the Pediatric Rheumatology European Society (PRES), the American College of Rheumatology (ACR), and the European League Against Rheumatism (EULAR), developed a new classification criteria to help standardize the conduct of clinical, epidemiological, and outcome research for this rare pediatric disease.[5] These criteria (Box 1), which will supplant the adult criteria [Table 1] that have been used until now, will help ensure an accurate diagnosis of JSSc.

Children under 16 years of age account for less than 5% of all cases of JSSc.[6] Peak age of onset is between 10 and 16 years.[7] In an Indian study, the mean age at presentation was 17 years.[8] The disease is almost fourfold more frequent in girls. Raynaud's phenomenon (RP) is the first sign of the disease in 70% of the patients, and in 10% it is complicated by digital infarcts. Proximal skin induration is the second most frequent symptom, being present in 40% of cases.[9]

Treatment

The pharmacologic management of patients who have JSSc is challenging, because no drug has been shown to be of unequivocal benefit in either children or adults who have systemic sclerosis. Patients with scleroderma require different therapeutic approaches depending on whether their disease is in an 'active' inflammatory stage, or a later 'irreversible' stage with fibrosis, but no active inflammation.[6] The main treatment modalities

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Box 1: Preliminary classification criteria for juvenile systemic sclerosis

Major criterion— Proximal sclerosis/indurations of the skin

Minor criteria

Skin
- Sclerodactyly

Vascular
- Raynaud's phenomenon
- Nailfold capillary abnormalities
- Digital tip ulcers

Gastrointestinal
- Dysphagia
- Gastro-esophageal reflux

Renal
- Renal crisis
- New-onset arterial hypertension

Cardiac
- Arrhythmias
- Heart failure

Respiratory
- Pulmonary fibrosis (high resolution computed tomography/ radiograph)
- Diffusing lung capacity for carbon monoxide
- Pulmonary hypertension

Musculoskeletal
- Tendon friction rubs
- Arthritis
- Myositis

Neurological
- Neuropathy
- Carpal tunnel syndrome

Serology
- Antinuclear antibodies
- SSc-selective autoantibodies (anticentromere, antitopoisomerase I, antifibrillarin, anti-PM-Scl, anti-fibrillin or anti-RNA polymerase I or III)

A patient, aged less than 16 years, shall be classified as having juvenile systemic sclerosis if the one major and at least two of the 20 minor criteria are present. This set of classification criteria has a sensitivity of 90%, a specificity of 96%, and kappa statistic value of 0.86. Source: Zulian (2008)

Table 1: Classification of the scleroderma disease spectrum

Systemic sclerosis

Diffuse cutaneous systemic sclerosis: Diffuse, systemic, skin fibrosis. Includes proximal limbs, trunk, and face. There is often early internal organ involvement.

Limited cutaneous systemic sclerosis (CREST syndrome). Distal skin involvement, later organ involvement.

Overlap syndromes: Skin tightness with features of other connective tissue diseases.

Localized scleroderma

Morphea: Circumscribed sclerotic patches with variable pigment changes.

Plaque morphea: Localized. Single or small areas involved.

Generalized morphea: Confluent or multiple regions.

Pansclerotic morphea: Widespread, symmetric distribution with superficial and deep involvement including muscles and tendons.

Linear scleroderma: Band-like distribution of fibrous pigmented skin, usually on extremities.

En coup de sabre: On face.

Parry-Romberg syndrome: Hemifacial atrophy of skin and tissues beneath forehead. Fascia is the primary target; skin is secondarily affected.

Eosinophilic fasciitis: Fascia is the predominant site of involvement; involves extremities but spares hands and feet.

CREST = Calcinosis, Raynaud's phenomenon, esophageal motility disorders, sclerodactyly, telangiectasia.

Source: Rosenkranz *et al.*[9]

currently used are antifibrotics, immunosuppressive agents, and vasodilators.[10] Several organ-specific therapies are also employed.

Antifibrotic agents: Massive deposition of collagen and other newly synthesized connective tissues leading to fibrosis may lead to organ failure in diffuse cutaneous systemic sclerosis (dcSSc). Antifibrotic agents have not been very successful in treating dcSSc.

Penicillamine is the oldest of the commonly used antifibrotic agents, but has lost favor among most rheumatologists. It has been used to treat dcSSc for several decades, but with questionable efficacy. In uncontrolled case series, penicillamine was beneficial, resulting in skin softening, a reduction of new visceral involvement, and improved survival.[11] A double-blind randomized controlled clinical trial concluded that low-dose penicillamine (125 mg alternate days) was of equivalent efficacy with that of high-dose administration (750-1000 mg/day) of the drug.[12] There are only anecdotal reports of penicillamine efficacy in children, and it is not commonly used any longer.

Interferon-γ is a cytokine that has been shown to reduce collagen production and interfere with fibroblast proliferation by downregulating the expression of transforming growth factor-β (TGFβ).[13] However, it has not been shown to be very effective and has a high incidence of adverse reactions, and is therefore not commonly used.

Another agent with a potential antifibrotic effect is relaxin, a pregnancy polypeptide cytokine growth factor that decreases the synthesis of interstitial collagens and blocks TGFβ *in vitro*.[14] Intially, this treatment showed promise in a randomized, double-blind, parallel-group, placebo-controlled, multicenter clinical trial,[15] but a phase II trial of relaxin was

negative and this treatment option was abandoned.[16]

Imatinib mesylate, a potent inhibitor of TGFβ as well as platelet-derived growth factor (PDGF), and thus the synthesis of extracellular matrix (ECM) proteins, has been shown to prevent experimental dermal fibrosis, thereby holding out new hope for antifibrotic management in systemic sclerosis.[17]

Immunosuppressive agents: Methotrexate, which is used widely for the treatment of many rheumatic conditions in children, has been shown to improve skin score in early dcSSc in adults.[18] A randomized controlled trial in early diffuse scleroderma in adult patients done in India showed that methotrexate produces a slight favorable effect, particularly on the skin scores; however, it is not sustained after 12 months.[19] Children tend to tolerate higher doses of methotrexate well and have very little toxicity associated with it.[20] According to a pediatric SSc experts' opinion, methotrexate could be the treatment of choice for the skin manifestations of children who have JSSc, especially in the early phase.[21] All children receiving methotrexate should be mentioned for adverse effects such as liver toxicity, pulmonary fibrosis and cytopenias.

Cyclosporin is a medication occasionally used to treat dcSSc in adults, but is more frequently used in children. Cyclosporin blocks the transcription of messenger RNA for several immnue-activating and proinflammatory cytokines (e.g. interleukin (IL)-2) that are elevated in dcSSC.[22] All trials of cyclosporin for dcSSc have been performed in adults. There continue to be reports of cyclosporin being used in children with dcSSc, though there have been no organized trials.[23] As with all medications, children should be monitored closely for adverse effects such as renal insufficiency and hypertension.

Glucocorticoids, preferably prednisone at a dosage of 0.3-0.5 mg/kg/d, have very few indications in JSSc; indications include the treatment of myositis, arthritis and tenosynovitis. Several studies suggest that steroids are associated with a higher risk of scleroderma renal crisis.[24] Therefore, patients on steroids should be monitored carefully for blood pressure and renal function.

Despite the modest benefits claimed in recently published studies,[25] and despite its known toxicity, an EULAR task force of 18 SSc international experts have recently opined that cyclophosphamide should be considered for the treatment of SSc-related interstitial lung disease in children.[4] As in juvenile systemic lupus erythematosus, cyclophosphamide should be administered as intravenous pulse therapy at a dosage of 0.5 to 1g/m^2 every four weeks for at least six months.[4] Adequate hydration and frequent voiding must be emphasized to prevent cystitis. Prophylatic MESNA should be considered to minimize contact of acrolein with the bladder mucosa.

UVA-1 phototherapy has recently showed some promise for treating the sclerotic skin lesions of systemic sclerosis, but its use in children is limited due to concerns about carcinogenicity; however, currently UVA-1 is considered less carcinogenic than psoralen plus UVA (PUVA).[26]

Intravenous immunoglobulin (IVIg) has been recently used as an immunomodulator and has been shown to reduce skin fibrosis in systemic sclerosis.[27] Likewise, tumor necrosis factor (TNF)-alpha blockers, notably infliximab and etanercept, have been investigated in recent years in diffuse scleroderma and has shown marginal clinical improvement, especially of skin involvement.[28] Prominent among other biologics to be used with some success in systemic sclerosis is rituximab, the CD-20 positive B-cell antagonist.[29]

Vasodilators: Vasodilators are used to reduce vasospasm (Raynaud phenomenon, RP) and to improve peripheral circulation in children with dcSSc. Although used regularly, those have been no trials of vasodilator treatments in children with scleroderma.

Calcium channel antogonists (CCA) are the vasodilators most often used to treat dcSSc. These drugs inhibit smooth muscle contraction by reducing the cellular uptake of calcium. Two groups of CCAs have been used: the pyridine dicarboxylic acids (nifedipine and nicardipine) and the dimethoxyphenyls (verapamil and diltiazem). Amlodipine is a newer agent that is being increasingly used. Oral CCAs should be considered as first-line therapy for RP.

Angiotensin II receptor inhibitors (e.g., losartan) have also been found to have benefit in the treatment of RP. Angiotensin converting enzyme (ACE) inhibitors (e.g., captopril) are unanimously considered to be effective for the long-term control of blood pressure

and stabilization of renal function of scleroderma renal crisis.

Prostacyclin analogues, intravenous prostanoids that is, are used for severe SSc-related RP and digital ulcers.[30] Intravenous epoprostenol is a potent vasodilator produced by endothelial cells that acts through activation of membrane-bound adenylate cyclase to increase cyclic adenosine monophosphate (cAMP). Iloprost (carboprostacyclin) is a chemically stable prostacyclin analogue. It is a potent vasodilator and has been shown to decrease connective tissue growth factor (CTGF) levels.[31] A recent study in children who had JSSc and other connective tissue diseases reported that intermittent infusions of iloprost was safe and effective in treatment of refractory RP and ischemic digits.[32]

Some recommendations for symptomatic treatment are essentially based on the principle of good clinical practice. These include the use of:

- Proton pump inhibitors (PPIs), such as omeprazole and lansoprazole, for preventing gastroesophageal reflux disease (GERD) and esophageal ulcers.
- Prokinetic drugs, such as domperidone, for managing symptomatic dysmotility.
- Rotating antibiotics, such as metronidazole, ciprofloxacin, and doxycycline, to treat malabsorption caused by bacterial overgrowth.[4]

Future therapies: Bosentan, a dual endothelin receptor antagonist, is a novel agent being experimented in pulmonary arterial hypertension (PAH), which carries the worst prognosis of any organ involvement in systemic sclerosis. This agent targets endothelin-1, a peptide with vasoconstrictive effects. Novel agents with vasodilator properties, like sitaxsentan and sildenafil, are being investigated for digital ulcers. Pediatric experts have expressed interest for future applications of these agents in pediatric clinical trials, although there is not enough experience, at present, to recommend their use. Other than these, several agents and classes of therapy are being investigated in adults [Table 2]; there is no idea, however, if and when these will be applicable in pediatric patients.

Conclusion: Compared with adult-onset disease, JSSc appears to be less severe with less organ involvement and to have less specific autoantibody profile and better long-term outcome. Many of the recommendations for the management of SSc in adults can be extended to the childhood-onset SSc. A few of the studies and trials on

Table 2: Experimental therapies in systemic sclerosis[26-28]

Broad spectrum immunomodulation
Mycophenolate mofetil
Rapamycin (sirolimus)
Intravenous immunoglobulin
Autologous hematopoietic stem cell transplantation
Targeted immunosuppression
Antithymocyte globulin
Tolerance to human type I collagen (oral bovine collagen I)
Recombinant human antitransforming growth factor-β1(TGFβ1) antibody (CAT-192)
Biologic therapies
Anti-tumor necrosis factor α
Infliximab
Etamercept
Anti-CD20
Rituximab
Tyrosine Kinase inhibitors
Imatinib mesylate
Dasatinib
Nilotinib
Histone deacetylase inhibitors
Trichostatin A
Extracorporeal photopheresis
Antifibrotic therapies
Minocycline
Interferons— interferon-α, interferon-γ
Vasodilators
α-adrenergic blockers— selective α_{2c} adrenoceptor blockade
Supplementation of L-arginine/nitric oxide pathway, including phophodiesterase inhibitors
Topical glyceryl trinitrate patch
Phosphodiesterase type 5 inhibitors (sildenafil, tadalafil)
Phosphodiesterase type 3 inibitor (cilostazol)
Serotonin antagonists
Serotonin receptor antagonist (ketanserin)
Selective serotonin reuptake inhibitor (fluoxetine)
Antioxidants
Probucol
Vitamin E
Allopurinol (blocks superoxide by way of xanthine oxidase)
Antithrombotics
Low-dose aspirin
Low molecular weight heparin
Tissue plasminogen activator/warfarin
Botulinum toxin
Surgery
Digital artery (palmar) sympathectomy
Decompression arteriolysis (of radial and ulnar arteries)
Angioplasty

None of the above therapies have been specifically investigated in the pediatric population of systemic sclerosis.

SSc mentioned in this review have been summarized along with their levels of evidence[33] in Table 3.

JUVENILE LOCALIZED SCLERODERMA

Juvenile localized scleroderma (JLS), also known as morphea, consists of a group of conditions that involve essentially the skin and subcutaneous tissues. JLS is much more common than systemic sclerosis in childhood, by a ratio of at least 10:1.[34] No studies have assessed the prevalence of this disease, but it is believed to occur in up to 1 per 100,000.[35] There is a mild female predilection (female to male ratio 2.4:1).[36] The mean age at disease onset is 7.3 years, and a few cases with onset at birth, so called congenital localized scleroderma, have been described.[37]

Table 3: Levels of evidence of systemic sclerosis therapies

First author, year, ref.	Interventions	Study population and sample size	Trial design description and follow-up	Level of evidence[33]	Main reported result
Clements, 1999[12]	High-dose vs low-dose D-penicillamine Group 1: 750-1000 mg/day *Group 2:* 125 mg every other day All were for 24 months	134 patients with early (<18 months) diffuse cutaneous scleroderma	Double-blind, randomized, parallel group study, 24 months	2b	No advantage in using D-pen at doses higher than 125 mg every other day
Grassegger, 1988[13]	IFN-γ vs control Group 1: IFN-γ Group 2: control	44 patients with type I/II scleroderma	Randomized, controlled, multicentre, parallel group trial	2b	Significant improvement of quality of life parameters in the control group but not in the treatment group
Seibold, 2000[15]	Placebo vs low-dose vs high-dose continuous subcutaneous infusion of recombinant human relaxin relaxin Group 1: Placebo Group 2: 25μg/kg/day Group 3: 100μg/kg/day	68 patients with stable, diffuse, moderate-to-severe scleroderma <5 years	Phase II, double-blind, randomized, placebo-controlled, parallel group trial, 4-24 weeks	2b	25 μg/kg relaxin resulted in significantly reduced skin thickening and other skin scores compared to placebo, but not the patients on 100 μg/kg/day
Krishna Sumanth, 2007[19]	Uncontrolled study of weekly oral methotrexate (15mg/wk)	33 Indian patients with systemic sclerosis, mean age 31.45 years	Uncontrolled open trial, 6 months	4	Methotrexate for 6 months only provides subjective improvement
Quartier, 2002[23]	Uncontrolled study with corticosteroid, methotrexate and cyclosporine combination	4 children with SSc, features of polymyositis and mild to severe dilated cardiomyopathy	Uncontrolled case series	4	Combination therapy did not impair progression of esophageal or myocardial dysfunction
Tashkin, 2006[25]	Oral cyclophosphamide (≤2 mg/kg/day) vs matching placebo for 1 year	158 patients with scleroderma with restrictive lung disease	Double-blind, randomized, placebo-controlled trial, 24 months	1b-	1 year of oral cyclophosphamide had a significant but modest benefit on lung function, dyspnea, thickening of skin, and health-related quality of life
Levy, 2004[27]	High-dose IVIg (2g/kg/ course) for 3-6 monthly courses	5 patients with limited and 10 patients with diffuse systemic sclerosis	Uncontrolled, open-label study, 6 months	4	Significant decrease in skin score and significant improvement in quality of life
Ellman, 2000[28]	Etanercept 25 mg subcutaneously twice weekly for 6 months	10 patients with diffuse scleroderma	Uncontrolled, open-label, pilot study,	4	Without control group, the clinical outcome data is inconclusive.
Pope, 2007[30]	5 trials compared i.v. iloprost, 1 studied p.o. iloprost and 1 p.o. cisaprost	332 patients with scleroderma	Systematic review of 7 randomized trials, 5 of them parallel-group.	1a	I.V. iloprost is efficacious in Raynaud's phenomenon secondary to systemic sclerosis.

Most commonly JLS is divided into five general types: plaque morphea, generalized morphea, bullous morphea, linear scleroderma and deep morphea.[38] A new classification has been proposed including the following five subtypes: circumscribed morphea (CM), linear scleroderma, generalized morphea (GM), pansclerotic morphea and the mixed subtype where a combination of two or more of the other subtypes is present.[39] JLS patients who have extracutaneous manifestations represent a new subset of JLS.

Investigational tools: Clinical examination in JLS being subjective, and classical skin scoring methods, viz., the modified Rodnan score used in systemic sclerosis being not applicable, the detection of disease activity remains a fundamental problem, that is now sought to be addressed by a few novel tools that, however, need to be validated.

Infrared thermography (IRT), that is of value in the detection of active JLS,[40] has a very high reproducibility but low specificity, particularly in the assessment of older lesions. In the latter, laser Doppler flowmetry (LDF) can help discriminate real active lesions from false-positive changes.[41] A computerized skin score (CSS) method for measuring circumscribed lesions in LS has been recently proposed.[42] CSS has been shown to have very low intra- and interobserver variability. Magnetic resonance imaging (MRI) is also an important tool, particularly when central nervous system (CNS) or eye involvement is suspected, as also to demonstrate the true depth of soft tissue lesions.[43]

In addition, there is evidence to suggest that laboratory measures such as eosinophilia, hypergammaglobulinemia or elevated ESR are signs of active disease.[44]

Therapy: JLS is a very slow, progressive disease. The usual natural history is to remit spontaneously over time. However, it may result in severe morbidity as well, limiting range of motion, atrophying the limb or face, deforming growth and causing leg length discrepancy Unfortunately, the rarity of this condition and the difficulty in assessing outcome in an objective manner have limited the interpretation of most clinical studies. As a result, no guidelines have emerged till now for the disease. In this scenario, the key determination is the level of discomfort (cosmetic or functional) associated with the developing lesion, which must be balanced against the risks of therapy.

Physiotherapy plays a major part in the management of LS, particularly in lesions involving articular structures. However, no published studies have documented this therapy.[9]

Topical therapy is indicated for lesions that neither involve the deeper structures nor are associated with significant cosmetic disability. Emollients are marginally effective in this setting.[45] Topical corticosteroids may be of some use during the inflammatory stage and in circumscribed morphea, but long-term use may cause subcutaneous atrophy. Intralesional corticosteroids have also been tried in JLS. Topical tacrolimus 0.1% ointment has been used for the treatment of early inflammatory morphea with some success.[46] In a clinical trial involving seven patients for three months, lesions treated with occlusive tacrolimus for 12 h at night, resulted in softening and reduced inflammatory infiltrate in all patients one month after treatment.[47] Topical calcipotriene (calcipotriol) has also been tried in CM.[48] Cunningham *et al*, evaluated the efficacy of calcipotriene ointment 0.005% in an open study of 3 months duration in 12 patients between 12 and 38 years of age. At the end of the study, the authors observed significant improvement of cutaneous induration in all patients and a lack of side effects and abnormalities in mineral metabolism. Good results have been reported recently with topical imiquimod, a novel immunomodulator that upregulates interferons α and γ, thereby downregulating TGFβ and inhibiting collagen production by fibroblasts.[49]

Despite the lack of knowledge on risks and benefits, vitamin D and its analogues (viz. calcitriol) have been utilized systemically in some studies of LS with mixed results. A randomized controlled trial of 20 adult patients with LS did not demonstrate efficacy of oral calcitriol.[50] However, in a study of seven children with LS treated with oral calcitriol (0.25-1.25 μg/day), five had skin improvement. No adverse effects were observed during a follow-up period of 4-20 months.[51]

Phototherapy with ultraviolet (UV) rays represents another therapeutic possibility in LS.[52] Treatment with UVA1 at low, medium, and high doses, without or with psoralens (PUVA) all seem to be effective clinically, though high doses seem somewhat better. Phototherapy appears to be much more effective for localized or superficial lesions. Although no controlled studies have been published, excellent results have been reported with PUVA treatment in patients with

localized scleroderma.[53] Pasic *et al,* reported the treatment of six children with photochemotherapy with PUVA baths with good results, showing softening of sclerotic plaques. The results were obtained with a small number of sessions (14-39, mean 25).[54] Grundmann-Kollmann *et al,* showed that topical PUVA induced significant improvement in 4 patients treated 4 times a week, totaling up to 30 sessions.[55] Because the rate of relapse after UV phototherapy discontinuation is not known, the need for prolonged maintenance therapy, leading to a high cumulative dosage of irradiation, and the increased risk for potential long-term effects such as skin aging and carcinogenesis are clear limitations for its use in the pediatric age group.[56]

When there is a significant risk of disability, such as in linear and deeper subtypes, methotrexate (MTX) in combination with systemic corticosteroids should be considered.[57] The treatment protocol usually consists of a combination of oral prednisolone or intravenous methylprednisolone (IVMP 20-30 mg/kg/d for 3 days) and MTX (10-15 mg/m^2/wk). Most patients show a response within two to four months, and the adverse effects are usually mild and associated more with steroid use rather than with MTX. Unfortunately, the studies have not been controlled trials, and the series of treated patients very small.[58]

Penicillamine appears to affect collagen metabolism and has been used to treat localized scleroderma for a long time.[59] Moynahan reported uniformly good results in all 14 children treated with low-dosage penicillamine (150-450 mg/day) with no adverse effects.[60] These results have been fairly corroborated by later studies as well.[61]

Conclusion: JLS is an uncommon challenging disorder. The rarity of scleroderma in the pediatric population plus the fact that this disease is very often self-limiting makes randomized controlled trials very difficult. It is for this reason that most data on treatment modalities for this disease have been extrapolated from studies in adult patients. There is no single therapy for JLS that has proven to be very effective or significantly disease

Table 4: Levels of evidence of therapies for localized scleroderma

First author, year, ref.	Interventions	Study population and sample size	Trial design description and follow-up	Level of evidence[33]	Main reported result
Stefanaki, 2008[46]	Tacrolimus 0.1% cream without occlusion twice daily for 4 months	13 patients with morphea	Uncontrolled, open-label trial, up to 1 year	4	Topical tacrolimus 0.1% cream is useful in morphea, particularly in early inflammatory lesions
Cunningham, 1998[48]	Calcipotriene 0.005% ointment under occlusion twice daily to morphea plaques for 3 months	12 patients aged 12-38 years having biopsy-proven morphea or linear scleroderma	Uncontrolled open-label study, 3 months	4	All 12 patients showed statistically significant improvement in all studied cutaneous parameters
Hulshof, 2000[50]	Calcitriol orally (0.75 µg/day for 6 months + 1.25 µg/day for 3 months) or placebo	27 patients (7 with SSc and 20 with morphea, 25 women, 2 men, aged 22.7-70.1 years)	Randomized, double-blind, placebo-controlled study, 9 months	1b	No benefit of calcitriol over placebo in morphea
Kreuter, 2006[52]	Low-dose UVA1 (20J/cm^2) or medium-dose UVA1 (50J/cm^2) or narrowband UVB, 5 times weekly for 8 weeks	64 patients with localized scleroderma	Prospective, open, randomized, controlled 3-arm study, 8 weeks	1b	Phototherapy is an effective therapeutic option in localized scleroderma.
Weibel, 2006[57]	Pulsed i.v. methylprednisolone followed by oral prednisolone on a reducing regimen and maintenance treatment with methotrexate	34 children with morphea	Open, uncontrolled retrospective study, mean follow-up 3 years	4	Systemic corticosteroids and methotrexate in combination are beneficial and well-tolerated in children with localized scleroderma.
Falanga, 1990[61]	D-penicillamine 2-5 mg/kg/day given over 15-53 months	11 children with severe, extensive localized scleroderma	Open, uncontrolled retrospective study	4	D-penicillamine may be effective in severe cases of localized scleroderma in children

modifying [Table 4]. However, current therapeutic strategies must be initiated early in the disease course for maximally beneficial clinical effects. The close collaboration among pediatricians, rheumatologists and dermatologists represents an important advance in the management of this disabling condition.[62]

REFERENCES

1. Doyle JA, Connolly SM, Winkelmann RK. Cutaneous and subcutaneous inflammatory sclerosis syndromes. Arch Dermatol 1982;118:886-90.
2. Belch JJ. The clinical assessment of the scleroderma spectrum disorders. Br J Rheumatol 1993;32:353-5.
3. Preliminary criteria for the classification of systemic sclerosis (scleroderma): Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 1980;24:581-90.
4. Zulian F. Systemic sclerosis and localized scleroderma in childhood. Rheum Dis Clin North Am 2008;34:239-55.
5. Zulian F, Woo P, Athreya BH, Laxer RM, Medsger TA Jr, Lehman TJ. The PRES/ACR/EULAR provisional classification criteria for juvenile systemic sclerosis. Arthritis Rheum 2007;57:203-12.
6. Scalapino K, Arkachaisri T, Lucas M, Fertig N, Helfrich DJ, Londino AV Jr, *et al*. Childhood-onset systemic sclerosis: Classification, clinical and serologic features, and survival in comparison with adult-onset disease. J Rheumatol 2006;33:1004-13.
7. Martini G, Foeldvari I, Russo R, Cuttica R, Eberhard A, Ravelli A. Systemic sclerosis in childhood: Clinical and immunological features of 153 patients in an international database. Arthritis Rheum 2006;54:3971-8.
8. Misra R, Singh G, Aggarwal P, Aggarwal A. Juvenile onset systemic sclerosis: A single center experience of 23 cases from Asia. Clin Rheumatol 2007;26:1259-62.
9. Rosenkranz ME, Agle LM, Efthimiou P, Lehman TJ. Systemic and localized scleroderma in children: Current and future treatment options. Paediatr Drugs 2006;8:85-97.
10. Sapadin AN, Fleischmajer R. Treatment of scleroderma. Arch Dermatol 2002;138:99-105.
11. Jimenez SA, Sigal SH. A 15-year prospective study of treatment of rapidly progressive systemic sclerosis with D-penicillamine. J Rheumatol 1991;18:1496-503.
12. Clements PJ, Furst DE, Wong WK, Mayes M, White B, Wigley F. High-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis: Analysis of a two-year, double-blind, randomized, controlled clinical trial. Arthritis Rheum 1999;42:1194-203.
13. Grassegger A, Scholer G, Hessenberger G, Walder-Hantich B, Jabkwski J, Macheiner W, *et al*. Interferon-gamma in the treatment of systemic sclerosis: A randomized controlled multicentre trial. Br J Dermatol 1988;139:639-48.
14. Unemori EN, Pickford LB, Salles AL, Piercy CE, Grove BH, Erikson ME, *et al*. Relaxin induces an extracellular matrix-degrading phenotype in human lung fibroblasts *in vitro* and inhibits lung fibrosis in a murine model *in vivo*. J Clin Invest 1996;98:2739-45.
15. Seibold JR, Korn JH, Simms R, Clements PJ, Moreland LW, Mayes MD, *et al*. Recombinant human relaxin in the treatment of scleroderma: A randomized, double-blind, placebo-controlled trial. Ann Intern Med 2000;132:871-9.
16. Seibold JR. Relaxins: Lessons and limitations. Curr Rheumatol Rep 2002;4:275-6.
17. Distler JH, Jungel A, Huber LC, Schulze-Horsel U, Zwerina J, Gay RF, *et al*. Imatinib mesylate reduces production of extracellular matrix and prevents development of experimental dermal fibrosis. Arthritis Rheum 2007;56:311-22.
18. Pope JE, Bellamy N, Seibold JR, Baron M, Ellman M, Carette S, *et al*. A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. Arthritis Rheum 2001;44:1351-8.
19. Krishna Sumanth M, Sharma VK, Khaitan BK, Kapoor A, Tejasvi T. Evaluation of oral methotrexate in the treatment of systemic sclerosis. Int J Dermatol 2007;46:218-23.
20. Foeldvari I. Scleroderma in children. Curr Opin Rheumatol 2002;14:699-703.
21. Zulian F, Kowal-Bielecka O, Miniati I, Avouac J, Chwiesko S, Aggarwal A, *et al*. Preliminary agreement of the Pediatric Rheumatology European Society (PRES) on the EUSTAR/EULAR recommendations for the management of systemic sclerosis in children [abstract]. Proceedings of the 14th Pediatric Rheumatology Congress. Istanbul (Turkey), September 5-9, 2007.
22. Needleman BW, Wigley FM, Stair RW. Interleukin-1, interleukin-2, interleukin-4, interleukin-6, tumor necrosis factor alpha, interferon-gamma levels in sera from patients with scleroderma. Arthritis Rheum 1992;35:67-72.
23. Quartier P, Bonnet D, Fournet JC, Bodemer C, Acar P, Ouachee-Chardin M, *et al*. Severe cardiac involvement in children with systemic sclerosis and myositis. J Rheumatol 2002;29:1767-73.
24. DeMarco PJ, Weisman MH, Seibold JR, Furst DE, Wong WK, Hurwitz EL, *et al*. Predictors and outcomes of scleroderma renal crisis: The high-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis trial. Arthritis Rheum 2002;46:2983-9.
25. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, *et al*. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006;354:2655-66.
26. Kroft EB, Berkhof NJ, van de Kerkhof PC, Gerritsen RM, de Jong EM. Ultraviolet A phototherapy for sclerotic skin diseases: A systematic review. J Am Acad Dermatol 2008;59:1017-30.
27. Levy Y, Amital H, Langevitz P, Nacci F, Righi A, Conforti L, *et al*. Intravenous immunoglobulin modulates cutaneous involvement and reduces skin fibrosis in systemic sclerosis: An open-label study. Arthritis Rheum 2004;50:1005-7.
28. Ellman MH, McDonald PA, Hayes FA. Etanercept as treatment for diffuse scleroderma: A pilot study. Arthritis Rheum 2000;43:S392.
29. Graves J, Nunley K, Heffernan M. Off-label uses of biologics in dermatology: Rituximab, omalizumab, infliximab, etanercept, adalimumab, efalizumab, and alefacept. J Am Acad Dermatol 2007;56:e55-79.
30. Pope J, Fenlon D, Thompson A, Shea B, Furst D, Wells GA, *et al*. Iloprost and cisaprost for Raynaud's phenomenon in systemic sclerosis. Cochrane Database Syst Rev 1998;2:CD000953.
31. Stratton R, Shiwen X, Martini G, Holmes A, Leask A, Haberberger T, *et al*. Iloprost suppresses connective tissue growth factor production in fibroblasts and in the skin of scleroderma patients. J Clin Invest 2001;108:241-50.
32. Zulian F, Corona F, Gerloni V, Falcini F, Buoncompagni A, Scarazatti M, *et al*. Safety and efficacy of iloprost for the treatment of ischaemic digits in paediatric connective tissue diseases. Rheumatology (Oxford) 2004;43:229-33.
33. Bigby M. The hierarchy of evidence. In: Williams H, editor. Evidence-based Dermatology, 2nd ed. Malden: Blackwell Publishing; 2008. p. 34-7.
34. Peterson LS, Nelson AM, Su WP, Mason T, O'Fallon WM, Gabriel SE. The epidemiology of morphea (localized scleroderma) in Olmsted county 1960-1993. J Rheumatol 1997;24:73-80.
35. Steen VD, Oddis CV, Conte CG, Janoski J, Casterline GZ, Medsger Jr TA. Incidence of systemic sclerosis in Allegheney County, Pennsylvania: A twenty-year study of hospital-diagnosed cases, 1963-1982. Arthritis Rheum 1997;40:441-5.
36. Zullian F, Athreya BH, Laxer RM, Nelson AM, Feitosa de Oliveira SK, *et al*. Juvenile localized scleroderma: Clinical and epidemiological features in 750 children: An international study. Rheumatology (Oxford) 2006;45:614-20.
37. Zulian F, Vallongo C, de Oliveira SK, Punaro M, Ros J, Mazur-

Zielinska H, *et al*. Congenital localized scleroderma. J Pediatr 2006;149:248-51.
38. Peterson LS, Nelson AM, Su WP. Classification of morphea (localized scleroderma). Mayo Clin Proc 1995;70:1068-76.
39. Zulian F, Ruperto N. Proceedings of the II Workshop on Juvenile Scleroderma Syndrome. Padua (Italy), June 3-6, 2004, quoted in Zulian (2008).
40. Martini G, Murray KJ, Howell KJ, Harper J, Atherton D, Woo P, *et al*. Juvenile-onset localized scleroderma activity detection by infrared thermography. Rheumatology (Oxford) 2002;41: 1178-82.
41. Wiebel L, Howell KJ, Visentin MT, Rudiger A, Denton CP, Zulian F, *et al*. Laser Doppler flowmetry for assessing localized scleroderma in children. Arthritis Rheum 2007;56:3489-95.
42. Zulian F, Meneghesso D, Grisan E, Vittadello F, Belloni Fortina A, Pigozzi B, *et al*. A new computerized method for the assessment of skin lesions in localized scleroderma. Rheumatology (Oxford) 2007;46:856-60.
43. Liu P, Uziel Y, Chuang S, Silverman E, Krafchik B, Laxer R, *et al*. Localized scleroderma: Imaging features. Pediatr Radiol 1994;24:207-9.
44. Uziel Y, Feldman BM, Krafchik BR, Yeung R, Laxer R. Methotrexate and carticosteroid therapy for pediatric localized scleroderma. J Pediatr 2000;136:91-5.
45. Guitart J, Greenberg M, Solomon LM. Localized scleroderma. In: Clements PJ, Furst DE, editors. Systemic Sclerosis. Baltimore: Williams and Wilkins; 1996. p. 65-79.
46. Stefanaki C, Stefanaki K, Kontochristopoulos G, Antoniou C, Stratigos A, Nicolaidou E, *et al*. topical tacrolimus 0.1% ointment in the treatment of localized scleroderma: An open label clinical and histological study. J Dermatol 2008;35:712-8.
47. Mancuso G, Berdondini RM. Localized scleroderma: Response to occlusive treatment with tacrolimus ointment. Br J Dermatol 2005;152:180-2.
48. Cunningham BB, Landells ID, Langman C, Sailer D, Paller A. Topical calcipotriene for morphea/linear scleroderma. J Am Acad Dermatol 1998;39:211-5.
49. Dytoc M, Ting PT, Man J, Sawyer D, Fiorillo L. First case series on the use of imiquimod for morphea. Br J Dermatol 2005;153:815-20.
50. Hulshof MM, Bouwes Bavinck JN, Bergman W, Masclee AA, Heickendorff L, Breedveld FC, *et al*. Double-blind, placebo-controlled study of oral calcitriol for the treatment of localized and systemic scleroderma. J Am Acad Dermatol 2000;43: 1017-23.
51. Elst EF, Van Suijlekom-Smit LW, Oranje AP. Treatment of linear scleroderma with oral 1, 25-dihydroxyvitamin D3 (calcitriol) in seven children. Pediatr Dermatol 1999;16:53-8.
52. Kreuter A, Hyun J, Stucker M, Sommer A, Altmeyer P, Gambichler T. A randomized controlled study of low-dose UVA1, medium-dose UVA1, and narrowband UVB phototherapy in the treatment of localized scleroderma. J Am Acad Dermatol 2006;54:440-7.
53. De Rie MA, Bos JD. Photochemotherapy for systemic and localized scleroderma. J Am Acad Dermatol 2000;43:725-6.
54. Pasic A, Ceovic R, Lipozencic R, Husar K, Susic SM, Skerlev M, *et al*. Phototherapy in pediatric patients. Pediatr Dermatol 2003;20:71-7.
55. Grundmann-Kollmann M, Ochsendorf F, Zollner TM, Spieth K, Sachsenberg-Studer E, Kaufmann R, *et al*. PUVA-cream photochemotherapy for the treatment of localized scleroderma. J Am Acad Dermatol 2000;43:675-8.
56. Setlow RB, Grist E, Thompson K, Woodhead AD. Wavelengths effective in induction of malignant melanoma. Proc Natl Acad Sci U S A 1993;90:6666-70.
57. Weibel L, Sampaio MC, Visentin MT, Howell KJ, Woo P, Harper JI. Evaluation of methotrexate and corticosteroids for the treatment of localized scleroderma (morphea) in children. Br J Dermatol 2006;155:1013-20.
58. Seyger MM, van den Hoogen FH, de Boo T, de Jong EM. Low-dose methotrexate in the treatment of widespread morphea. J Am Acad Dermatol 1998;39:220-5.
59. Kesler RW, McDonald TD, Balasubramaniam M, Saulsbury FT. Linear scleroderma in children. Am J Dis Child 1981;135:738-40.
60. Moynahan EJ. Penicillamine in the treatment of morphoea and keloid in children. Postgrad Med J 1974;50:39-41.
61. Falanga V, Medsger Jr TA. D-penicillamine in the treatment of localized scleroderma. Arch Dermatol 1990;126:609-12.
62. Zulian F. Scleroderma in children. Pediatr Clin North Am 2005;52:521-45.