Cosmetic treatment in patients with autoimmune connective tissue diseases

Best practices for patients with morphea/systemic sclerosis

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Learning objectives
After completing this learning objective, the reader will be able to better discuss cutaneous manifestations of chronic cutaneous lupus erythematous, specifically discoid, panniculitis, profundus and tumidus and review the physiological and psychological burden of these diseases; identify and compare different laser treatments, injectables, and surgical options for cutaneous deficits attributable to these diseases; and recognize how to minimize side effects when performing cosmetic procedures on this special patient population.

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Morphea and systemic sclerosis are inflammatory, sclerosing disorders. Morphea primarily affects the dermis and subcutaneous fat, while systemic sclerosis typically involves the skin and internal organs. Functional impairment and cosmetic disfigurement are common in both diseases. Treatment options to mitigate disease progression remain limited. Both functional impairment and cosmetic deficits negatively impact quality of life and psychological well-being in this patient population. While the number of cosmetic procedures performed in the United States continues to rise each year, limited data exist regarding best practices for correcting aesthetic deficits caused by autoimmune conditions. There is scarce information to guide safety decisions regarding laser parameters, soft tissue augmentation, treatment intervals, and the concurrent use of immune-modifying or immune-suppressing medications. Given the fears of disease reactivation and exacerbation from postprocedural inflammation along with limited data, it is difficult for clinicians to provide evidence-based cosmetic treatment with realistic expectations with regard to short- and long-term outcomes. In the first article in this continuing medical education series, we attempt to address this practice gap. (J Am Acad Dermatol 2020;83:315-41.)

Key words: calcium hydroxylapatite; fat transfer; hyaluronic acid; injectables; intense pulsed light; mental health; morphea; poly-L-lactic acid; polymethylmethacrylate; pulsed dye laser; quality of life; systemic sclerosis.

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Abbreviations used:

ECDS:	en coup de sabre
HA:	hyaluronic acid
IPL:	intense pulsed light
MDD:	major depressive disorder
MHISS:	Mouth Handicap in Systemic Sclerosis
PDL:	pulsed dye laser
PRS:	Parry–Romberg syndrome
QoL:	quality of life
SSc:	systemic sclerosis

EPIDEMIOLOGY AND OVERVIEW OF MORPHEA/SYSTEMIC SCLEROSIS SUBTYPES

Key points

- Clinical findings of morphea include sclerotic plaques and possible involvement of fat and bone
- Cutaneous findings of systemic sclerosis include taut skin, sclerodactyly, microstomia, dyspigmentation, telangiectasia, calcinosis cutis, and cutaneous ulcers

Morphea and systemic sclerosis are inflammatory, sclerosing disorders. Morphea primarily affects the dermis and subcutaneous fat, while systemic sclerosis (SSc) typically involves the skin and internal organs. Functional impairment and cosmetic disfigurement are common in both diseases. Treatment options to mitigate disease progression remain limited.[1,2] Both functional impairment and cosmetic deficits negatively impact quality of life and psychological well-being in this patient population.

Morphea

Morphea is divided into several subtypes and typically evolves from an early inflammatory phase to skin sclerosis and subsequent atrophy.[3-6] Between 1960 and 1993, the annual incidence of morphea was 2.7 per 100,000 people, with 56%, 20%, 13%, and 11% having plaque-type, linear, generalized, and deep morphea, respectively.[7]

Plaque (or circumscribed) morphea. Plaque (or circumscribed) morphea is the most common variant of morphea and typically presents as an erythematous or hyperpigmented plaque. With time, the plaque center becomes sclerotic and centrifugally expands[6] (Fig 1).

Linear morphea and Parry–Romberg syndrome. Linear morphea is characterized by sclerotic plaques in a linear distribution. Morphea en coup de sabre (ECDS) is a type of linear morphea that involves the head and scalp. Some include Parry–Romberg syndrome (PRS) or progressive hemifacial atrophy, a condition characterized by unilateral atrophy of the skin, soft tissues, and underlying structures, as a variant of linear morphea.[6]

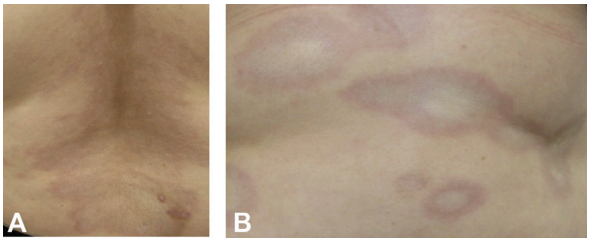

Fig 1. Plaque type morphea.

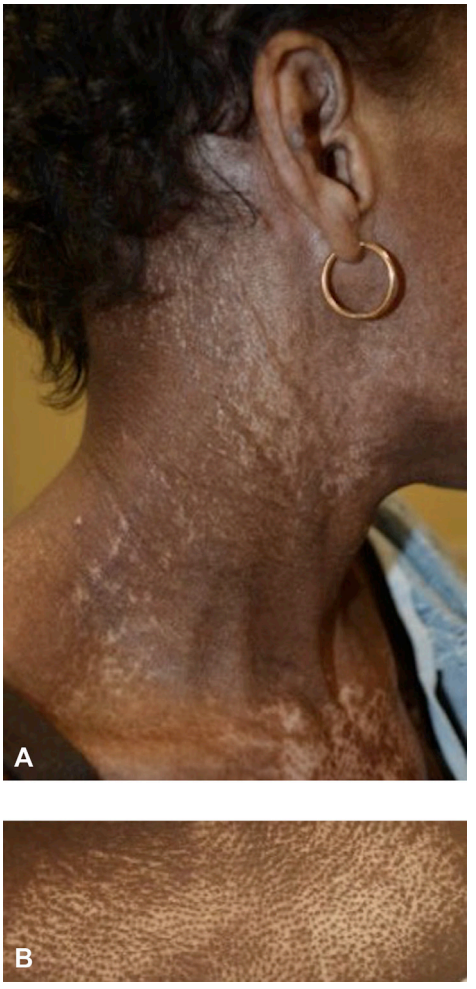

Fig 2. Scleroderma-associated dyspigmentation. **A**, Leukoderma (or "salt and pepper" pigmentation) of scleroderma on lateral neck of patient with Fitzpatrick skin phototype V to VI. **B**, Close-up of leukoderma of scleroderma of patient with Fitzpatrick skin phototype V to VI skin.

Generalized morphea. The generalized morphea subtype is defined as ≥4 morphea plaques occurring over ≥2 anatomic sites. Generalized morphea can be distingued from SSc due to lack of

Table I. Pulsed dye laser for morphea and systemic sclerosis

Authors/ Study type	N	Disease	Age/ skin type	Treatment/ location	Settings	Cooling/ postoperatively	Sessions/ interval	Perioperative medication	Results	Follow-up	Side effects
Eisen and Alster[92] case report	1	Plaque type morphea	41	Long pulse PDL to submandibular area	Wavelength: 585 nm, power/ fluence: 5 J/cm^2, pulse size: 1.5 ms, spot size: 10 mm	Dynamic epidermal cooling 30 ms	4 at 2-month intervals	NR	Subjective improvement after each session with improved pliability and skin coloration	6 months	None
Ciatti et al[93] case series	8	Scleroderma telangiectasia	36-71, disease duration of 3-20 years	PDL of face and neck	Wavelength: 585 nm, power/ fluence: 5-7 J/cm^2, pulse size: 0.45 ms, spot size: 5 mm	NR	1-4 sessions, interval NR	NR	Subjective efficacy, no evidence of adverse effect on disease progression	6 months-2 years	Purpura lasting 7-10 days
Dinsdale et al[25] RCT	19	SSc (limited n = 17, diffuse n = 2)	49-72, disease duration 2-31 years (mean 14)	PDL and IPL on face and upper limbs	PDL settings wavelength: 595 nm, power/ fluence: 9 J, pulse: 1.5 ms, spot size: 7 mm	Integrated cooling spray, 30 ms duration, 20-ms delay for pulse	3 (plus 1 spot test), 4-week interval	NR	PDL had greater improvement than IPL at week 16 for photographs and dermoscopy; no difference in red or green laser Doppler imaging between PDL/IPL at any time; more patients preferred PDL	8 weeks - 7 months from last session	Transient bruising
Halachmi et al[26] retrospective case control study	16	Scleroderma or CREST (n = 16), control group (n = 20)	21-67 (mean 37.4 years) Fitzpatrick skin phototypes II-IV	PDL on nose, neck, chest, and cheeks	Wavelength: 585 nm, power/ fluence: 5.5-7 J/cm^2, single pulse of 0.45 ms,	External cooling device	1-8, interval NR	NR	1.92 sessions needed for control group, 3.24 sessions needed for experimental group; all	NR	NR

Continued

Table I. Cont'd

Authors/ Study type	N	Disease	Age/ skin type	Treatment/ location	Settings	Cooling/ postoperatively	Sessions/ interval	Perioperative medication	Results	Follow-up	Side effects
					spot size: 5-7 mm				patients had 95% clearance; no significant association between outcome, energy fluence, anatomic site, age, or gender; lesion size was significant for no. of treatments needed		

CREST, Calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; *PDL*, pulsed dye laser, *IPL*, intense pulsed light; *NR*, not reported; *SSc* systemic sclerosis, *RCT*, randomized controlled trial.

hand involvement, absence of the Raynaud phenomenon, and early truncal lesions.[6]

Uncommon variants of morphea. Uncommon morphea variants include guttate morphea, atrophoderma of Pasini and Pierini, deep morphea, and keloidal morphea.[6]

Systemic sclerosis (limited and diffuse)

The annual incidence and prevalence of SSc in the United States is approximately 20 and 275 cases per million, respectively.[3] The differentiation between limited and diffuse SSc depends upon the degree of skin involvement. Limited SSc involves the distal extremities and the face, while diffuse SSc involves both distal and proximal extremities, the trunk, and the face.[8] Both subtypes may involve internal organs, most frequently the lungs, joints, and gastrointestinal tract. Cutaneous involvement typically begins with an edematous phase followed by sclerosis and then gradual atrophy. Other cutaneous features of both include microstomia, dyspigmentation (Fig 2), and telangiectasia. End-stage SSc of the fingers can result in contracted fingers, often with distal ulcerations and autoamputations and occasionally calcinosis.[4] According to the 2013 American College of Rheumatology Classification Criteria for SSc, thickening of the skin on the fingers of both hands extending proximal to the metacarpophalangeal joints is sufficient for a patient to be classified as having SSc irrespective of truncal lesions.[9]

IMPACT ON QUALITY OF LIFE AND PSYCHOLOGICAL WELL-BEING

Key points

- Systemic sclerosis/morphea may have a mild to severe impact on quality of life
- Major depressive disorder is common in patients with SSc and the prevalence varies among studies

Mental health

Both SSc and morphea may impact quality of life (QoL) in several ways, including physical symptoms, such as pain, pruritus, sensation of skin tightening, fatigue, myalgias, and arthralgias. Mobility limitations, cosmetic appearance, sleep disturbances, and impaired sexual function may also occur, leading to social and emotional distress.[10-12] There are limited data in the published literature, however, related to the specific impact of cosmetic disfigurement on QoL in these patients.

Of the instruments used to measure QoL in patients with morphea, both the Dermatology Quality of Life Index and Skindex-29[13] are examples

Table II. Intense pulsed light therapy for morphea and systemic sclerosis

Authors/ study type	N	Disease	Age/ skin type	Treatment/ location	Settings	Cooling/ postoperative	Sessions/ interval	Perioperative medication	Results	Follow-up	Side effects
Comstedt et al,[30] 2012 case series	4	SSc with microstomia	37-61, diagnosed 10-17 years earlier	IPL to perioral and cheeks	Wavelength: 530-570 mm?; power/ fluence: 11-14 J/cm^2; pulse size: 10-14 pulse durations	NR	3-6 at 4-week intervals	None	Oral opening increased 1 mm per treatment; patients described subjective softening of skin and easier speaking, eating, and tooth brushing	4 months	Transient moderate erythema and edema
Onesti et al,[27] 2009 case report	1	PRS	40, disease duration 19 years	Customized PLLA filler, lipofilling, and IPL to face	NR		3, interval NR	NR	Subjective improvement of hyperpigmentation, flattening of skin lesions, patient satisfied	12 months	NR
Dinsdale et al,[25] 2014 randomized within-subject trial	19	SSc (limited n = 17, diffuse n = 2)	49-72, disease duration 2-31 years (mean 14)	PDL and IPL on face and upper limbs	IPL settings: wavelength: 550-1100 nm; power/ fluence: 28-30 J/cm^2; each pulse had 2 shots with 20-ms delay	Delivered through US gel, postoperative cooling with water	3 (plus 1 spot test), 4-week interval	NR	PDL had greater improvement than IPL at week 16 for photographs and dermoscopy; no difference in red or green LDI between PDL/IPL at any time, and more patients preferred PDL	8 weeks-7 months from last session	None
Murray et al,[28] 2012 open study	17	SSc limited and diffuse	37-69 (median 58) Fitzpatrick types: I (n = 12), II (n = 7)	IPL to cheek, forehead, upper arm, and hand	Wavelength: 550-1100 nm, peak of 585 nm; power/ fluence: 24-36 J/cm^2 depending on skin type; pulse size:	Ice water before and after treatment for 5 min, IPL delivered through US gel	3 (plus 1 spot test), 1 month interval	NR	6-month images graded "no change" (n = 4), "improved" (n = 8), or "much improved" (n = 4); significant decrease in perfusion measured with LDI compared	6-12 months after last session	Facial edema, transient hyperpigmentation in Fitzpatrick IV patient (withdrew from study), blistering on dorsal surface of hand after

Continued

Table II. Cont'd

Authors/ study type	N	Disease	Age/ skin type	Treatment/ location	Settings	Cooling/ postoperative	Sessions/ interval	Perioperative medication	Results	Follow-up	Side effects
					2-6 ms duration, 10-30 ms delay				with baseline at 1- and 6-month follow-ups, but not at 12 months; improvement not maintained in all patients, suggesting need for further treatments		third session (n = 1)

IPL, Intense pulsed light; *LDI*, laser Doppler imaging; *NR*, not reported; *PDL*, pulsed dye laser; *PLLA*, poly-L-lactic acid; *PRS*, Parry–Romberg syndrome; *RCT*, randomized controlled trial; *SSc*, systemic sclerosis; *US*, ultrasound.

of skin-specific health-related QoL questionnaires. The short-form health survey is an instrument used to measure general health-related QoL.[14] The Localized Scleroderma Assessment Tool is a morphea-specific questionnaire comprised of 2 domains, a modified localized skin severity index and the localized scleroderma damage index.[15] Both tools are commonly used to measure disease severity. Factors demonstrated to have the greatest impact on QoL include disease severity, female sex, adult patients,[16] generalized disease,[13] being on systemic therapy, and hand and foot involvement.[10] Although patients with linear morphea reported a mild effect on QoL, about one-third of patients reported physical limitations that might not have been captured by the QoL tool used.[17] A retrospective study evaluating the QoL in a small cohort of adolescents with PRS reported a negative impact on QoL, especially within the appearance and emotional subscales. After surgical intervention, 80% of patients were extremely to somewhat satisfied with the surgical outcome and would consider another intervention or recommend surgery to those with a similar condition.[18]

The prevalence of major depressive disorder (MDD) in patients with SSc varies with the population studied, the questionnaire score used, and disease duration, ranging from 4% to 65%,[19,20] and appears to be higher in patients who are hospitalized.[21] A Russian study reported a much higher prevalence (83%) of mental disorders among patients with SSc, including MDD (67.3%), dysthymia (30%), and recurrent depressive disorder (31%).[22] While most patients are diagnosed with mild MDD and have episodes of low mood that may not require treatment, active monitoring is recommended.[23] Moreover, the unpredictable course of SSc and fear of disease progression may generate anxiety disorders.[11] Access to and management of health care resources may be an additional source of stress for patients with SSc because of diagnosis delays, multiple referrals, insurance coverage, and treatment cost.[24]

USE OF LASER AND LIGHT-BASED THERAPY

Key points

- Pulsed dye laser and intense pulsed light have been used to treat telangiectasias of morphea and systemic sclerosis, which may require more treatment sessions compared with nondisease telangiectasias
- Objective functional improvements have been reported after treatment with IPL and CO_2 laser for microstomia and joint contractures

Table III. Ablative and nonablative laser treatment for morphea and systemic sclerosis

Authors/ study type	N	Disease	Age/skin type	Treatment/ location	Settings	Cooling/ postoperative	Sessions/ interval	Perioperative medication	Results	Follow-up	Side effects
Kineston et al,[33] 2011 case study	1	Generalized morphea	27	CO_2 laser on leg	Wavelength: 10.6 μm; density: 5%; power/fluence: 50 mJ pulse; single pulse; pass/overlap: single pass, no overlap	Forced cooling system/dilute vinegar compresses BID and petrolatum TID	1	MTX 20 mg/week, topical calcipotriene 0.005% BID, intralesional triamcinolone acetonide, UVA1 phototherapy	Regained full plantar flexion of foot, decreased pain	1 year	None
Bottomley et al,[36] 1996 case series	6	Digital calcinosis of SSc	36-78, disease duration of 4-10 years	CO_2 laser on fingers	Power/fluence: 7.5-10 W; continuous wave mode; spot size: 1 mm	NR	1	None	Improvement seen 8-16 weeks postoperatively. Of 21 calcinoses treated, complete resolution in 12, partial improvement in pain in 5, no improvement of pain in 2. Calcinosis recurred within 3-4 months in 2 lesions. Overall, 3 patients had good response, 2 moderate, and 1 had no response	Median: 20 months	Postoperative infection in 2 patients 2 weeks after, treated with erythromycin (moderate results in both patients); mean healing time 4-10 weeks. 4 lesions had residual hyperkeratosis, remaining 17 had good cosmetic result
Chamberlain and Walker,[37] 2003 case report	1	Limited scleroderma	40	CO_2 laser on fingers	Power/fluence: 13-16 W, 3 mm scan; paint mode; spot size: 125 mm	NR	6 sessions over 5 years	NR	Subjective significant remission	3 years	6-week healing time
Apfelberg et al,[38] 1998 case series	3	Generalized systemic scleroderma	60-66, disease duration 5-30 years	CO_2 laser on perioral rhytides	Power/fluence: 300 mJ/60 W; pass/overlap: 3 full passes + 2 passes over raised "shoulders," 30% overlap	Dilute vinegar soaks 5-6 times/day starting postoperative day 3	1	Prophylactic antiviral agents 2 days before treatment, continued until epithelialization complete	Subjective satisfactory wound healing with cosmetic improvement	12-18 months	None; epithelialization complete in 7-10 days, erythema for 8-10 weeks
Bennani et al,[32] 2016 case series	4	Diffuse SSc (n = 2), sclero-myositis (n = 1), CREST (n = 1)	43-63, sclerosis present for ≥5 years Fitzpatrick type: II (n = 2), III (n = 1), IV (n = 1)	Pulsed CO_2 Laser on peri-oral area	125 mm hand piece Power/Fluence: 7W Pulse: 0.39 ms Spot size: 5 mm Pass/overlap: 2-3 passes until contraction of dermis, no overlapping	2% sodium fusidate ointment and petroleum jelly TID without dressing	1-3 sessions, 8- to 12-month intervals	Hydroxychloroquine 200 mg/day (n = 1), CCBs, PPIs, and pulmonary HPTN drugs for other symptoms	Mean interincisor distance gain: 8.5 mm (37% improvement, range 7-10 mm), mean MHISS decrease: 14 points (11-17); no change in modified Rodnan skin score	12 months	Transient erythema (15 days resolved) and dyschromia (90 days resolved)

Continued

Table III. Cont'd

Authors/ study type	N	Disease	Age/skin type	Treatment/ location	Settings	Cooling/ postoperative	Sessions/ interval	Perioperative medication	Results	Follow-up	Side effects
St Surin-Lord and Obagi,[94] 2011 case report	1	Scleroderma, polymyositis and lupus	35	High peak power Nd:YAG on hand ulcers from Raynaud's	Wavelength: 1064 nm; power/fluence: 10-15 J/cm^2; pulse size: 0.3 ms pulse width at 10 Hz; spot size: 5 mm; 5k-7k pulses/session	No cooling	11 sessions, 2-week intervals	NR	Patient reported satisfaction, ability to close hand, fewer Raynaud's attacks, and improved nail growth	NR	NR
Shalaby et al,[35] 2016 RCT intraindividual parallel study	21	Plaque (n = 12) and linear (n = 3) morphea, ECDS (n = 2)	7-47 years with disease duration 6-96 months, active disease in n = 7, Fitzpatrick type: III (n = 10) and IV (n = 7)	CO_2 laser vs. UVA1 phototherapy (each patient had ≥2 similar lesions that were randomized to 1 of the 2 treatments)	Power: 25 W; stack 2 dwelling time: 500 msec; spacing: 500 μm	NR	3 sessions with 1-month interval	None	Significantly improved LoSCAT score in CO_2 arm (2.65) compared with UVA1 arm (4.24), significantly higher patient satisfaction score in CO_2 arm (2.24) compared to UVA1 arm (1.12), significantly better collagen homogenization scores on histopathologic examination in CO_2 arm		Hyperpigmentation (n = 1), persistent erythema (n = 1), mild-moderate (n = 17) and marked (n = 10) pain
Chodkiewicz et al,[95] 2018 case report	1	Diffuse systemic scleroderma	42	Nd:YAG endovascular ablation to leg ulcer followed by sclerotherapy	Wavelength: 1320 nm; power: 6 W; frequency: 50 Hz	20-30 mm Hg compression stockings all day for 3 days, waking hours for following 7 days	1 session	NR	Resolution of ulcer	12 months	None

BID, Bis in die; *CCB*, calcium channel blocker; *CREST*, calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; *ECDS*, en coup de sabre; *HPTN*, hypertension; *LDI*, laser Doppler imaging; *LoSCAT*, Localized Scleroderma Assessment Tool; *MHISS*, Mouth Handicap in Systemic Sclerosis; *MTX*, methotrexate; *Nd:YAG*, neodymium-doped yttrium aluminum garnet; *NR*, not reported; *PPI*, proton pump inhibitor; *RCT*, randomized controlled trial; *SSc*, systemic sclerosis; *TID*, ter in die; *US*, ultrasound; *UVA1*, ultraviolet A1 light phototherapy.

Table IV. Strength of recommendations for laser treatment for morphea and systemic sclerosis

Recommendation	Recommendation no.	Level of evidence	Studies
Treatment of telangiectasias in this patient population may require more treatment sessions compared with nondisease telangiectasias	1.1	IIB	Halachmi et al[26]
For treatment of telangiectasias in patients with systemic sclerosis, patients may prefer the outcomes of PDL compared with IPL	1.2	IIB	Dinsdale et al[25]
IPL can be used to treat morphea- or systemic sclerosis–associated microstomia	1.3	III	Comstedt et al[30]
CO_2 laser can be used to treat morphea-related			
Heel contractures	1.4	III	Kineston et al[33]
Digital calcinoses	1.5	III	Bottomley et al[36] and Chamberlain and Walker[37]
Perioral rhytids and microstomia	1.6	III	Bennani et al[32] and Apfelberg et al[38]
Plaque, linear, and ECDS morphea	1.7	IB	Shalaby et al[35]

Level IA evidence includes evidence from metaanalysis of randomized controlled trials; level IB evidence includes evidence from ≥1 randomized controlled trial; level IIA evidence includes evidence from ≥1 controlled study without randomization; level IIB evidence includes evidence from ≥1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.
ECDS, En coup de sabre; *IPL*, intense pulsed light; *PDL*, pulsed dye laser.

Pulsed dye laser (PDL), via its targeted photothermolysis of hemoglobin, is an effective treatment for vascular lesions like port wine stains, hemangiomas, and telangiectasias, with potential side effects including pain, bruising, edema, hypopigmentation, and scarring.[25] The telangiectasias of SSc have been described as treatment resistant, perhaps because of the thicker capillary walls associated with collagen vascular diseases.[26] This theory is supported by a small-scale retrospective study showing that, regardless of size, 1.92 (range 1-5) PDL sessions were needed to treat the control group's telangiectasias compared with 3.24 (range 1-8) sessions that were needed to treat telangiectasias in patients with SSc.[26]

In addition to PDL, intense pulsed light (IPL) therapy can be used to treat telangiectasias via broad spectrum light that induces vessel coagulation through evenly distributed heat energy to capillary walls (Tables I and II).[25,27,28] A randomized split-face trial comparing PDL and IPL for treatment of telangiectasias in patients with SSc found that 50% of patients (n = 8) preferred the results of PDL treatment at 16 weeks of follow-up compared with 25% (n = 4) that preferred IPL results.[25]

In addition to telangiectasia treatment, IPL can induce collagen formation, which has been used in the treatment of microstomia.[29] Treatment of the perioral region with IPL has led to objective improvement in oral opening and subjective improvement in ease of speaking, eating, and tooth brushing.[30] Microstomia can also be improved with mouth opening and elongation exercises; however, improvement is typically lost upon discontinuation of these exercises.[31]

Fractional[32] and fully ablative lasers can be used to treat skin fibrosis associated with morphea and SSc (Table III). It has been postulated that immediate improvement after treatment is related to mechanical loosening of sclerotic tissue,[33] with delayed improvements arising from tissue response and upregulation of growth factors and cytokines that modulate healing.[34,35] CO_2 laser has been used to treat morphea-related heel contractures,[33] digital calcinoses,[36,37] and perioral rhytids[32,38] with good improvement. A randomized study showed CO_2 laser to be superior to phototherapy for various morphea types, including active disease.[35] A summary of treatment recommendations is provided in Table IV.

INJECTABLES

Key points

- Skin fibrosis in morphea and systemic sclerosis can create difficulty with initial injections but appears to improve over subsequent sessions
- Although there are no documented cases of disease reactivation of stable morphea after injectable treatment, caution should still be taken because most patients described in the published literature had reportedly inactive disease

Table V. Fat transfer for morphea and systemic sclerosis

Authors/ study type	N	Age	Disease	Treatment	Location/amount	Sessions/ interval	Perioperative medication	Result	Side effects	Follow-up
Zanelato et al,[96] 2013 case report	4	17-26	PRS	Fat transfer	Chin/NR	1 session	NR	Immediate subjective improvement	No one experienced hematomas	>1 year
Roh et al,[81] 2008 retrospective review	20	Age at procedure: 10-55 (mean: 26.3), disease duration: 1-15 (mean: 6.8 years), all disease was clinically inactive	LS	Fat transfer	Forehead, chin, infraorbital, nose; injected in multiple planes until slight over correction	2-11 (mean 4.2) with 3-month intervals	NR	51-75% subjective improvement of forehead, <25% improvement chin, fair correction infraorbital, poor correction nose; no changes in hyper- or hypopigmentation or telangiectasias	Minimal bruising, pain, edema, and erythema for <72 hours	12-94 months (age 43)
Oh et al,[97] 2003 case report	1	21 at procedure, 6-year disease history, 2 years stable	Trilinear scleroderma ECDS	Autologous "tissue cocktail"	Forehead, overcorrected until convex	1 session	NR	Excellent cosmetic results; almost level with surrounding tissue, hyperpigmentation disappeared	None	14 months
Sautereau et al,[59] 2016 longitudinal open label study	14	Mean age 53.8 at procedure, mean disease duration 9.4 years	SSc, 6 limited, 8 diffuse	Microfat grafting	Face, mouth; mean: 16.3 mL, median was 17 mL	1 session	Steroids <10 mg/day (n = 3), mycophenolae mofetil (n = 1), mycophenolae mofetil + steroid <10 mg/day (n = 1), methotrexate (n = 1), methotrexate + steroid <10 mg/day (n = 1)	Improvement in mouth pain, oral opening, and sicca; 75% of patients satisfied or very satisfied; mean 34.6% MHISS improvement from baseline at 6 months; 79.5% and 65.3% improvement of skin sclerosis at 3 and 6 months, respectively; no correlation between improvement and amount of injected fat	Harvest site bruising (n = 8) and pain (n = 3); injection site bruising (n = 3), pain (n = 3), perioral sensitive manifestation (n = 1), and trigeminal neuralgia (n = 1), all mild and spontaneously resolved in a few days	6 months, 1 patient refused, 1 died of unrelated cause
Gheisari et al,[45] 2018 open label study	16	29-54 at procedure, disease duration 4-10 years	SSc, 6 limited, 10 diffuse	Autologous fat transfer; Coleman technique but gravity separation	Face, mouth: 15-40 mL	NR	Taking prednisolone >10 mg/d was exclusion criteria	62.5% patients very satisfied, 12.5% somewhat satisfied, 18.75% unsatisfied due to total resorption at 3 months but maintained improvements in mouth opening and function; improvements on MHISS (−6.12) and Rodnan (−0.5) scores; no significant change in Cutaneous Resonance Running Time value	Bruising at harvest site reported by 10 patients, spontaneously resolved within 2 weeks	3 months
Del Papa et al,[98] 2015 prospective study	20	Median age 36.5 years and median 8 years of disease duration	Diffuse SSc	Autologous fat transfer; Coleman technique	8 different perioral areas; 2 mL per site, mean 16 mL total	1 session	None for 3 months prior	Increased inter-incisional distance (mean increase 2.63 mm at 3 months), oral perimeter (9.2 mm at 3 months), and neovascularization; 80% very satisfied, 20% rather satisfied; partial restoration of skin structure based off	Small ecchymosis that resolved in 2 weeks	3 months

								number and appearance of dermal papillae; neoangiogenesis confirmed via videocapillaroscopy and immuniohistologic changes		
Clauser et al,[99] 2011 retrospective cohort	2	Mean age 38	PRS	Coleman technique fat graft	NR	Mean 1.6 sessions, interval NR	NR	Subjective improvement in facial morphology, function, shape, and volume, as well as quality and texture of skin	Partial necrosis of tip of nose, unclear if this occurred in either of the PRS patients	14 months
Hammer-Hansen et al,[100] 2015 case report	1	9	LS	Fat transfer, Coleman technique	Face, 14, 22, 36 mL per session respectively	3, interval NR	NR	Good subjective results with volume retention, no further progression of mandibular atrophy, skin hyperpigmentation remains unchanged	NR	22 months
Hunstad et al,[101] 2011 case report	1	9, disease active stage	PRS	Coleman technique microfat grafting	Malar, mandible, chin: 13 mL total	1 session	NR	Stable results at 2-month follow-up except parasymphyseal prejowl region which was going to require additional treatments; disease process halted after treatment	Patient underwent a growth spurt with significant weight gain and grafted areas became very hypertrophic and had to be reduced by liposuction	4 years
Clauser et al,[66] 2010 case report	1	15	PRS	Structural fat grafting with PLLA revision	Cheek, chin: 30-75 mL per session	5 sessions over 3-year period	NR	After first procedure, gradual atrophy recurrence over frontal bone; complete patient satisfaction 15 months after second procedure	NR	3 years from first procedure
Avelar et al,[102] 2010 case report	1	42 at procedure, PRS started at 23, inactive since 30	PRS	Autologous fat transplant + auricular cartilage graft to chin	First session: 30 mL buccal, 20 mL zygomatic, 15 mL preauricular, 10 mL oral rim, 10 mL mentum; second session: 35 mL buccal, 15 mL zygomatic, 10 mL preauicular; expected small degree of resorption	2- with 6-month interval	NR	Subjective facial symmetry	NR	18 months since first procedure
Guerrerosantos et al,[85] 2007 case series	4	20-40	PRS	Lipoinjection	Face, 10-60 mL per session	1-4 sessions with 6- to 12-month intervals	NR	Subjective excellent aesthetic improvement	NR	6 months-8 years
Sterodimas et al,[103] 2009 case report	1	26 at procedure, disease stable for 8 years	PRS	Autologous fat transfer	Zygomatic, pre-auricular, buccal, mandible, mentum: 155 mL	1 session	NR	Subjective symmetry, some absorption noted at 13 months, patient declined additional procedure	Swelling resolved in 1 week	13 months
Yang et al,[61] 2016 case series	27	16-31 at procedure, mean age of onset: 10.1, mean duration of atrophy: 7.2	PRS	Fat transfer	Face: mean total: 133.61 mm^3; did not overcorrect to avoid oil cysts and necrosis	2-5 sessions (mean 3.1), interval NR	NR	Mean satisfaction score: immediate postoperatively = 4.3, 3 months postoperatively = 4.1, 12 months postoperatively = 4.0; mean fat absorption ratio was 47.92%	None	12-15 months (mean 13.6)

Continued

Table V. Cont'd

Authors/ study type	N	Age	Disease	Treatment	Location/amount	Sessions/ interval	Perioperative medication	Result	Side effects	Follow-up
								measured by 3D laser technology		
Jiang et al,[42] 2016 retrospective study	13	Mean 33	PRS	3L3M fat transfer	Face: means: 30.3 mL first session, 23.2 mL second session	2 sessions, 6-month (n = 12) or 1 year (n = 1) intervals	NR	Significant increase in patient (3.8-4.6) and surgeon satisfaction scores after second treatment compared with first; with 3D laser scan, first graft survival 43.3%, second graft survival 75.1%, despite no significant difference in injected volume	None	3 months
Alencar et al,[104] 2011 case report	1	38 at procedure with active disease, 15 at disease presentation	PRS	Autologous fat graft	Face, 50 mL per session	2 with 2-month interval	NR	High subjective patient satisfaction	NR	6 months
Consorti et al,[105] 2012 case report	1	34	ECDS	Autologous fat graft	Forehead: session amounts: first: 39 mL, second: 30 mL, third: 40 mL	3, interval NR	NR	Subjective improvement in frontoorbital symmetry, morphology, and tissue atrophy and texture	NR	2 years
Magalon et al,[60] 2015 case report	1	57	SSc	Autologous fat graft	Perioral: 19.8 mL	1 session	Low-dose steroids, methotrexate, folic acid, nifedipine, bosentan, and esome-prazole and emollient creams BID	MHISS: 36 to 23; xerostomia inventory index 52 to 44; sugar test 4:00 to 2:54; mouth opening 25 to 35 mm	None	6 months
Ho-Asjoe et al,[106] 1996 case report	1	41	SSc	Autologous fat graft + free dermal graft	Fat graft: naso-labial fold; dermal graft: vermillion border; amount NR	1 session	NR	Subjective patient satisfaction	NR	6 weeks
Palmero et al,[18] 2010 retrospective chart review	17	Mean 15 at procedure, mean 6.14 years from diagnosis	12 ECDS, 5 PRS	Fat injection (ECDS 9, PRS 5), poly-ethylene implant (ECDS 6, PRS 2), bone paste cranioplasty (ECDS 2, PRS 2), scar revision (ECDS 3, PRS 1), groin flap (ECDS 2), rhinoplasty (ECDS 1, PRS 1), canthoplasty (PRS 2)	NR	1-4, interval NR	Calcipotriol (n = 3), MTX (n = 6), pulse steroids (n = 1), oral steroids (n = 3), topical steroids (n = 1), topical Vitamin A (n = 2), mycofenilate (n = 1), IVIG (n = 1)	1/10 "Extremely satisfied," 4/10 "very satisfied," 3/10 "somewhat satisfied," 1/10 "not too satisfied," 1/10 "not at all satisfied"	Fat necrosis (1, ECDS)	1-9 years
Longobardi et al,[107] 2011 case report	1	Presented at 23, remission at 41, procedure at 50	PRS	Autologous fat graft + facial rejuvenation (rhytidectomy)	40 mL total, 5 mL buccal, 10 mL zygomatic, 10 mL preauricular, 5 mL orbital rim, 10 mL mental	1 session	NR	Excellent subjective results with no additional transplant necessary	NR	4 years
Slack et al,[62] 2013 retrospective controlled study	42	NR	PRS	Autologous fat transfer (most patients had received additional surgical interventions)	Face: mean volume was 48 ± 3.3 mL per session; and a mean total volume was	Means: mild disease 1.8, moderate: 3.4, severe: 5.2, overall:	NR	3D photogrammetry system showed fat preservation after 1 year was 19.5 ± 2.0 mL (40%) in PRS patients, 81% in	6% complication rate, which included bleeding, wound infection, diplopia, eyelid ptosis, hardware failure, corneal	5.3-28.8 years (mean 8.5)

					155 ± 5.1 mL (after mean 3.3 procedures)	3.2. Mean treatment span was 4.2 years			control group. Mean symmetry score of 68% preoperatively and 94% postop. Skin color and texture scores improved from 2.4 ± 0.06 to 3.4 ± 0.09 postoperatively; melanin index improvement of ≥15% was seen in all fat-grafted patients and an improvement of ≥50% was seen in 64% of fat-grafted patients; mean melanin index improvement seen in the diseased regions of Romberg patients after fat grafting was 42%	abrasion, and delayed wound healing, though unclear what procedures led to these complications; no donor-site morbidity	
Rodby et al,[108] 2016 case report	1	15, stable for 2 years	PRS	Coleman technique autologous fat transfer	Malar, nasolabial fold, lips, buccal, mental, mandible; first session: 30 mL, second: 45 mL, goal was 10-15% overcorrection	2 with 2-month interval	NR	3D photos to assess symmetry; subjective improvement in skin quality, color, suppleness, volume and natural expression; improved ease of injection at second session; stable at follow-up	NR	2 years
Agrawal et al,[90] 2015 case report	1	19 at surgery, 6 when disease started, stable since 17	PRS w/ECDS, type 3 per Guerrero Santos classification	Autologous fat graft + cartilage graft into sub periosteal space in forehead	First session: 15 mL forehead, 1.5 mL supraorbital rim, 5 mL temple, 5 mL zygoma, 10 mL mandible, 5 mL chin; second session: 5 mL zygoma, 1.5 mL supraorbital, 2 mL infraorbital	2 with 6-month interval	NR	Stable and satisfactory result	Minimal hairline scar from cartilage graft	15 months since second procedure
Van der Cruyssen et al,[109] 2018 retrospective	1	47	PRS	Fat transfer	Perioral: amount NR	NR	NR	Stable results with perioral muscular strength regained	NR	3 years
Cortese et al,[110] 2000 case series	2	NR	PRS, 1 severe, 1 moderate	Autologous fat graft (severe patient had primary temporal bone & muscle flap and zygomatic augmentation procedures)	Cheek, zygomatic bridge; used 20% overcorrection in session 1, based overcorrection for next sessions on amount resorbed in first	3 with 3-month intervals	NR	80% fat resorption for severe case, 75% for moderate case, measured clinically and echographically; subjective complete correction patient satisfaction.	NR	6 months
Lee et al,[86] 2017 case report	1	21 with 8 years disease duration	Localized scleroderma	Fat graft	Forehead, cheek: amount NR	NR	MTX	Subjective deformity resolution; among 6 scleroderma cases studied, no recurrences after 5 years of follow-up	Minor postoperative scarring	2 years 3 months
Moscona et al,[111] 1989 case report	1	34 at procedure, disease started at 16 and stable since 24.	PRS	Fat transfer	Face. 100 mL in 1st session.	4 with 4- to 6-week intervals	NR	Subjective; no further resorption of fat, good facial expression, patient satisfied	Marked edema that resolved in 14 days	18 months from last injection

Continued

Table V. Cont'd

Authors/ study type	N	Age	Disease	Treatment	Location/amount	Sessions/ interval	Perioperative medication	Result	Side effects	Follow-up
Xie et al,[112] 2007 case series	31	19-28 (mean 23.5), disease stable for at least 1 year	PRS	Autologous fat transfer	3-14 mL mandibular, 5-25 mL buccal, 2-10 mL zygomatic, goal was 20-30% overcorrection	1 (n = 15), 2 (n = 13, all moderate disease), 3 (n = 3, all severe disease). 3- to 6-month intervals	NR	At 6 months, >65% of patients assessed as satisfactory by all 3 groups (patient, surgeon, layperson), 10-30% mostly satisfactory, <7% unsatisfactory; most volume on postoperative day 7, reduced continuously until 3 months, then stable in long term; hyperpigmentation was noticeably improved; direct correlation between the severity of hemi facial atrophy and the requirement for multiple treatments	None	Mean after last injection, 2.06 years
Roddi et al,[113] 1994 case series	6	16-41 (mean 25.7) at surgery, 12-40 years stable (mean 21)	PRS	Microfat lipofilling	Face: 20-60 mL total, 1 mL amounts, 1 layer only subcutaneously	NR	NR	Subjective satisfactory results	NR	NR
Chajchir and Benzaquen,[114] 1989 case series	9	20-70	Scleroderma (n = 3), PRS (n = 6)	Fat graft injection	Parieto, temporal, mandibular areas: 50-120 mL, 30-50% overcorrection	5 for PRS, 4 for SSc, interval NR	NR	Unable to assess	Edema, hematoma	NR
Denadai et al,[43] 2018 prospective randomized study without control	53	Mean 27.1	PRS	Coleman technique autologous fat graft	Forehead, chin, and cheek. Mean 13.8 mL initial procedure, mean 12.4 mL repeat procedures	2 sessions, interval at 3, 6, or 12 months by random assortment	NR	Significant decrease of injected volume during initial 3 months, stable volume following 3 months; no significant difference in intergroup (second fat graft performed at 3 vs. 6 vs. 12 months after initial graft) secondary graft retention; significantly higher graft retention rate for second procedure across all 3 groups at 3, 6, and 12 months postoperatively	Self-resolving swelling and bruising	12 months
Harp et al,[115] 2018 case report	1	28	PRS	Autologous fat injection	Right hemiface: session 1: 12.5 mL, session 2: 20 mL, session 3: 46 mL	3 sessions at 4- to 5-month intervals	NR	Patient satisfied	NR	NR
Mura et al,[40] 2018 case report	1	40	Linear morphea	Autologous fat transfer	Upper limb	3 sessions at 6-month intervals	None	Patient reported immediate improvement of paresthesia, eventual improvement of tissue consistency and flexibility	None	NR

BID, Bis in die; *ECDS*, en coup de sabre; *IVIG*, intravenous immunoglobulin; *LS*, linear scleroderma; *MHISS*, Mouth Handicap in Systemic Sclerosis; *MTX*, methotrexate; *NR*, not reported; *PLLA*, poly-L-lactic acid; *PRS*, Parry—Romberg syndrome; *SSc*, systemic sclerosis.

Table VI. Cell-assisted injectables for morphea and systemic sclerosis

Author/study type	N	Age	Disease	Treatment	Location/amount	Sessions/ interval	Perioperative medication	Results	Side effects	Follow-up
Blezien et al,[46] 2017 prospective study	7	31-65, mean = 46.3; mean disease duration was 10 years	SSc	Microfat graft with PRP	Lips, 3 mL total with no overcorrection	NR	NR	Mean 0.6-cm increase in oral opening; 11.94% increase lower lip and 8.47% upper lip increased thickness; mean 5.28 decrease in MHISS score; focal reduction in dermal fibrosis in 5/7 patients	Graft area edema (3%), harvesting site ecchymosis (5%), and postoperative pain >3 days (11%)	12 months
Scuderi et al,[116] 2013 prospective trial	6	Age: 18-41; age of onset: 4-12; no active disease for ≥6 months	Generalized morphea with psoriasis (n = 1), linear scleroderma (n = 2), ECDS (n = 1), linear and plaque scleroderma (n = 2, 1 of which also had SLE)	8×10^5 ASCs per 1 mL of HA filler	Face, arm, upper limb: <10 mL total	1	No immune-modifying drugs within 4 weeks; no topical meds within 2 weeks except emollients	Arrest of disease progression (n = 6), regression of dyschromia (n = 4), erythema reduction (n = 1), skin softening (n = 5), better subjective skin sensitivity (n = 4); patients extremely satisfied (n = 4), moderately (n = 1), and satisfied (n = 1)	Small ecchymosis	12 months
Virzi et al[117] 2017 prospective study	6	Age: 41-63; disease duration 3-20 years	Diffuse cutaneous SSc	ADMSCs + PRP	Perioral	NR	No immune-modifying drugs	Elasticity increased 16.64% for lip, 17.80% for cheek; marked improvement in opening and extension of labial rhyme; increased capillary density (n = 4) and decreased vascular ectasia (n = 2)	NR	3 months
Onesti et al[118] 2016 controlled trial	10	Age: 23-48; disease duration 3-18 years; stable for 1-16 years	Diffuse cutaneous scleroderma	Fat transfer (n = 5) vs ADMSCs with HA (n = 5)	6 perioral areas, 2 mL per site, 16 mL total	2 sessions with 3-month interval	No immune modifying drugs within 4 weeks; no topicals within 2 weeks except emollients	Significant improvement in mouth opening and Italian version MHISS score within each group, insignificant difference between groups; patient satisfaction in fat transfer group, 80% rather satisfied, 20% very satisfied; in ADMSC group, 80% very satisfied, 20% rather satisfied	NR	12 months
Cervelli and Gentile,[47] 2009 case report	2	Age: 25, 50; disease duration 12, 38 years	PRS	Autologous fat lipostructure + PRP	Zygomatic region: 20 -55 mL, cheek: 5-35 mL, buccal rime: 10-25 mL, upper eye-lid: 3-5 mL, temporal area: 5-45 mL, supraorbital area: 3-13 mL	1-2 sessions with 4-month interval	NR	Obtained desired thickening of skin, but not facial contour filling	NR	NR
Koh et al,[49] 2012 RCT	10	Mean age: 28	PRS	Microfat graft vs microfat graft with 1×10^7 ADMSC	9.3-22.5 mL session 1, 3.2-7.4 mL session 2, 30% overcorrection	2 sessions with 14-day interval	NR	Measurements with 3D camera and CT showed 20.59% resorption in stem cell group, 46.81% resorption in graft alone group; mean patient satisfaction was higher in experimental group than in control group	Exaggerated volume loss on treated hemiface in 1 patient after intentional 15-kg weight loss	Mean follow-up 15 months
Karaaltin et al,[50] 2012 case report	1	19 year old, 4 year disease duration	ECDS	Autologous fat graft + ADMSC	Forehead, amount NR	2 sessions, 1-year interval	NR	Result at 1 year was satisfactory for the patient but required an additional session	None	1 year

Continued

Table VI. Cont'd

Author/study type	N	Age	Disease	Treatment	Location/amount	Sessions/ interval	Perioperative medication	Results	Side effects	Follow-up
Ortega and Sastoque,[48] 2015 case report	1	12-year-old, disease started at 5, previous free flap surgery at 8	PRS	Integra filler + fat transfer with PRP + realignment of latissimus dorsi flap	Face, amount NR	1 session	NR	Symmetry maintained as determined by CT imaging; histopathologic examination showed integra filler had integrated into soft tissues; patient satisfied	None	2 years
Chang et al,[51] 2013 controlled trial	20	Mean age 27.5; stable disease for ≥1 year	PRS	Fat graft vs fat graft + stromal vascular fraction	Mandibular: 5-20 mL per session; buccal: 4-30 mL per session; zygomatic: 3-12 mL per session; 0.5 mL per injection site, goal was 10-20% overcorrection	1-3 sessions with 6-month intervals	NR	At 6 months, fat survival was 68.3% in SVF group vs 58.5% in fat alone group; facial volumes increased until postoperative days 10-14, then reduced until 3 months postoperatively, after which volume remained stable; subjective improvement of skin color at injection site	None	At least 1.5 years after the first injection, and 1 year after last injection
Castro-Govea et al,[52] 2012 case report	1	35 years old, 10-year disease history, 5 years stable disease	PRS	Fat transfer with ADMSC	15 mL temporal, 25 mL cheek, 3 mL lips, 15 mL malar, 35 mL mandible/base of neck	1 session	NR	Subjective improvement in volume, skin quality, texture, and elasticity	NR	1 and 12 months
Jianhui et al,[55] 2014 controlled trial	36	Fat only group: age 18-38; MSC group: 20-35; all in stable phase for ≥1 year	PRS	Fat graft (n = 26) vs fat graft with bone marrow MSCs (n = 10)	Face, 4-32 mL per session, goal was 2-30% overcorrection	1-3 sessions with 6-month intervals	NR	In fat only group, satisfactory symmetry obtained after 1 session (n = 12), 2 sessions (n = 8), and 3 sessions (n = 4), 1 patient had unsatisfactory result; in MSC group, symmetry after 1 session (n = 10); most volume on postoperative day 7; volume decreased until 3 months postoperatively and then remained stable	1 patient from fat only group had to undergo liposuction to correct overcorrection	Mean follow-up after last session was 14 months
Yoshimura et al,[53] 2008 prospective study	1	Age: 35	PRS	CAL	110 mL total into the face	NR	None	Excellent subjective improvement (80% improvement or better)	Subcutaneous bleeding that resolved in 1-2 weeks; swelling resolved in 4 weeks	13 months
Chen et al,[44] 2018 case series	11	18-29, disease duration 3-15 years	Scleroderma	CAL	Forehead (4-30 mL), cheek (10-45 mL), lip (4-20 mL), chin (2-15 mL)	1 (n = 4), 2 (n = 3), 3 (n = 3), 4 (n = 1), previous flap surgery (n = 3), interval 5-29 months	Chronic systemic corticosteroids (n = 5) for 3-10 years	Patient satisfaction VAS (1-10) at 6 months postoperatively, nonsteroid cohort: 5, 7, 8, 8, 8, 9; steroid cohort 6, 6, 6, 7, 9; also compared ADMSCs from patients and n = 10 healthy control liposuction patients; significant cell growth delay and decrease in total cell number in corticosteroid cohort compared with healthy controls and	None	6 months

								nonsteroid-treated scleroderma patients		
Almadori et al,[54] 2019 case series	62	Mean: 56, mean disease duration 15 years, all with stable disease for ≥2 years	SSc (diffuse n = 26, limited n = 36)	Lipotransfer with added ADMSC	Nose, cheeks, chin, nasolabial folds, lips	Mean 3 sessions (range 1-10)	MMF (n = 14), MTX (n = 6), other nonspecified immune-suppressing medication (n = 11), none (n = 31)	6.85 reduction in MHISS score, with significant decreases in all 3 subsets (mouth opening, sicca syndrome, aesthetic concerns. Significant improvement in all PROM (VAS, DAS24, BFNES, HADS-A, HADS-D); in all analysis, no difference based on immunosuppression status or SSc subtype, but differences between number of fat transfer sessions (≤2 vs ≥3); injected volume retention: cheeks (93.7%), nasolabial folds (81.9%), nose (67.4%), chin (68.2%), upper lip (35.5%), lower lip (27.3%)	Bruising, swelling, tenderness resolving in 14 days; 1 case of recipient site infection treated with oral antibiotics	Mean 12.4 months (range 6-53 months)

ADMSC, Adipose-derived mesenchymal stem cell; *ASC*, adipose stem cell; *BFNES*, Brief Fear of Negative Evaluation Scale; *BID*, bis in die; *CAL*, cell-assisted lipotransfer; *CT*, computed tomography; *DAS24*, Derriford Appearance Scale; *ECDS*, en coup de sabre; *HA*, hyaluronic acid; *HADS-A*, Hospital Anxiety and Depression Scale-Anxiety; *HADS-D*, Hospital Anxiety and Depression Scale-Depression; *LS*, linear scleroderma; *MHISS*, Mouth Handicap in Systemic Sclerosis; *MMF*, mycophenolate mofetil; *MSC*, mesenchymal stem cell; *MTX*, methotrexate; *NR*, not reported; *PLLA*, poly-L-lactic acid; *PRP*, platelet-rich plasma; *PRS*, Parry—Romberg syndrome; *RCT*, randomized controlled trial; *SLE*, systemic lupus erythematosus; *SSc*, systemic sclerosis; *SVF*, stromal vascular fraction; *VAS*, visual analog scale.

Reconstructive treatment with the use of fillers and injectables has become an increasingly common method of restoring the postinflammatory contour changes associated with morphea. Despite the theoretical risk of disease reactivation because of trauma from injection, to our knowledge there are no reports of disease reactivation after injectable use in this patient population. The majority of patients with documented morphea who underwent cosmetic injectable treatment had inactive disease at the time of injection and were not taking immune-modifying medications (Tables V-VIII). In addition, we did not find any reports of vascular compromise or skin necrosis among 488 cases of injectable use in patients with morphea or SSc.

Fat transfer

Autologous fat transfer has long been a preferred method for facial volume augmentation given that fat is easily accessible, versatile, and biocompatible.[39,40] However, it has been hypothesized that the combination of chronic inflammation,[41] poor environment at the recipient site,[42,43] and corticosteroid use[44] makes fat transfer in patients with morphea and SSc more subject to degradation. While some studies have shown this hypothesis to be true, fat transfer still represents an important treatment modality. Functional oral improvements appear to persist even in patients in whom transferred fat has been completely resorbed.[45] Some authors have attempted to improve unpredictable fat survival by augmenting traditional fat transfers with added cellular cultures including platelet-rich plasma,[46-48] adipose-derived mesenchymal stem cells,[44,49-54] or bone marrow—derived mesenchymal stem cells.[55] Mesenchymal stem cells are multipotent progenitor cells that are capable of differentiating into mesenchymal tissue[49] and that are hypothesized to have angiogenic and immunomodulatory effects.[46,56,57]

Although the majority of the published literature on fat transfer in the autoimmune patient population is based on subjective outcome measures, few studies have also demonstrated objective improvement after fat transfer by using the Mouth Handicap in Systemic Sclerosis (MHISS) scale,[45,46,54,58-60] computed tomography, and 3-dimensional (3D) imaging (Table V).[42,54,61,62] The MHISS Scale is a reliable and validated scale for assessing mouth opening impairment, sicca symptoms, and aesthetic concerns in SSc patients, with higher scores (maximum score 48) correlating with more severe symptoms.[58]

CT, ultrasound,[43] 3D photogrammetry, and 3D laser imaging have been used to evaluate the percentage of fat transfer "take," meaning the amount of

Table VII. Poly-L-lactic acid filler for morphea and systemic sclerosis

Authors/ study type	N	Disease	Treatment	Processing	Amount	Postprocedure	Sessions/interval	Result	Side effects	Follow up
Onesti et al,[65] 2009 case series	6	PRS (n = 2), LS (n = 4) all inactive disease	PLLA	Dilution ratio with sterile water ranged from 1:5-1:8	1-6 mL total per session, 0.1-0.2 mL per infiltration spaced 0.5 cm apart via 25-26 G needles, 30-40° angles, tunneling technique for lower face, depot technique for upper face	Ice compress before and after treatment, facial massage postoperatively to prevent subcutaneous nodules, patient at-home massage BID for 14 days	3-5 sessions at 4-week intervals	Subjective improvements in volume, symmetry, skin quality, hyperpigmentation (PRS only); all patients satisfied	Edema (n = 4), erythema (n = 4), submucous nodule (n = 1, due to infiltration error, removed surgically), postinjection bleeding (n = 1), pain (n = 1), palpable but not visible nodule (n = 1)	18 months
Clauser et al,[66] 2010 case report	1	PRS	Structural fat grafting with PLLA revision	NR	NR	NR	5 sessions total over 3-year span, last 2 with PLLA	Subjective good aesthetic outcome with complete patient satisfaction	NR	15 months after second session
Grimaldi et al,[68] 2008 case report	1	Inactive PRS	Poly-G-lactic acid + autologous fat transfer	Diluted in 8 mL sterile saline for superficial planes, in 3 mL for deeper planes	NR	NR	3 sessions, interval not reported other than 8 months between last poly-G-lactic acid treatment and fat transfer	Obtained desired thickening of skin but not filling effects (thus pursued fat transfer); patient satisfied but future fat transfers planned	NR	NR
Onesti et al,[27] 2009 case report	1	PRS	PLLA + lipofilling + IPL laser therapy	Diluted in 6 mL sterile water	Amount not reported, used 27G needle into deep derma or superficial hypoderm	Massaged PLLA after every 3 infiltrations	4 sessions at 4-week intervals	Stable result at follow-up; patient satisfied with volume, contours, and resolution of sclerosis and hyperpigmentation	No recurrences or complications	1 year

BID, Bis in die; *IPL*, intense pulsed light; *LS*, linear scleroderma; *NR*, not reported; *PRS*, Parry—Romberg syndrome; *PLLA*, poly-L-lactic acid.

Table VIII. Hyaluronic acid filler for morphea

Authors/study type	N	Disease	Treatment	Processing	Amount	Postprocedure	Sessions/interval	Result	Side effects	Follow-up
Choksi and Orringer,[71] 2011 case report	1	Inactive ECDS	UVA phototherapy followed by HA filler	NR	1 mL in linear threading technique	NR	2 sessions at 5-month intervals	Subjective >90% improvement of original defect; patient pleased	NR	NR
Thareja et al,[119] 2013 case report	1	Inactive ECDS	HA filler	NR	2 vials per session intradermal	NR	2 sessions at 6-month intervals	Patient satisfied; areas of scar tethered to underlying structures did not respond	None	7 months from first session
Sivek and Emer,[72] 2014 case report	1	ECDS	24 mg/mL HA filler premixed with anesthetic	23 G cannula made entry point for 25 G blunt-tipped microcannula, retrograde linear threading into preperiosteal plane	<1 mL	Light massage then ice packs	1 session	Patient satisfied with immediate results, declined future treatments	NR	9 months
Arsiwala,[120] 2015 case report	1	Focal scleroderma (circumscribed morphea) inactive for 5 years	20 mg/mL 1000 μm particle size HA filler	30 G needle, bolus injection technique	1 mL	Ice compresses and hand molding	1 session	Patient satisfied	None	9 months
Watchmaker et al,[73] 2019 case report	1	Bilateral PRS	HA filler, methotrexate 10 mg weekly	NR	NR	NR	NR	Subjective significant improvement	No apparent disease progression	2 months

ECDS, En coup de sabre; *HA*, hyaluronic acid; *NR*, not reported; *PRS*, Parry–Romberg syndrome; *UVA*, ultraviolet A light phototherapy.

Fig 3. Parry–Romberg syndrome (**A**) before and (**B**) after hyaluronic acid injection to the cheek and midface. The patient underwent serial injections spaced 4 to 12 weeks apart. **C**, Patient with Parry–Romberg syndrome before treatment with hyaluronic acid. **D**, Patient with Parry–Romberg syndrome immediately after treatment with hyaluronic acid filler to the left temple.

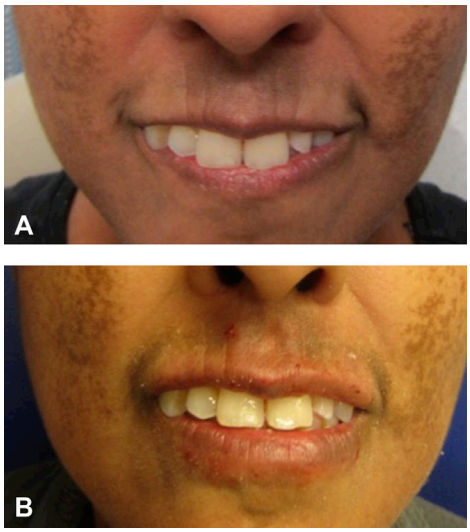

Fig 4. Lips of a patient with systemic sclerosis (**A**) before and (**B**) immediately after hyaluronic acid injection.

injected fat that successfully incorporates with surrounding tissue and persists at long-term follow-up.[42,61,62] One study using 3D photogrammetry found that "final fat take" at 1-year follow-up was 40% in patients with PRS compared with 81% in the control group. They recommended more treatment sessions with greater overcorrection margins when performing fat transfer for PRS (level of evidence IIA).[62]

It has been hypothesized that progressive improvement in skin elasticity with repeated fat transfer decreases tension and improves fat graft survival. This theory is supported by a study that showed increase in fat graft survival rate based on 3D laser imaging on repeated fat injection (43.3% and 75.1% fat survival after the first and second procedures, respectively).[42] A recent case series of patients with diffuse (n = 26) and limited (n = 36) SSc found significant differences in improvements in MHISS and multiple patient-reported outcome measures based on the number of fat transfer sessions, further supporting the hypothesis that multiple sessions of fat transfer could provide cumulative benefit (level of evidence III).[54]

Poly-L-lactic acid

Poly-L-lactic acid (PLLA) is a biocompatible, immunologically inert synthetic polymer that stimulates fibroblast proliferation[63] and thus collagen formation[27,64] improving both skin quality and

Table IX. Calcium hydroxylapatite or polymethyl methacrylate filler for morphea

Authors/study type	N	Disease	Treatment	Processing	Amount	Postprocedure	Sessions/interval	Result	Side effects	Follow-up
Franco et al,[76] 2016 case report	1	Stable ECDS	PMMA 10-30% filler	Thin cannula with 10% PMMA for forehead, injected retrograde crossed in X; thicker cannula with 30% PMMA for scalp	NR	NR	3 sessions with 3-month intervals	Patient satisfied, partial hair regrowth at site of previous disease related alopecia	NR	NR
Cox and Soderberg,[77] 2010 case report	1	Inactive PRS	CaHA and HA filler	Serial fanning with retrograde injection in the subcutaneous plane	2.6-3.9 mL CaHA to right hemiface, 1 mL HA infraorbital	NR	5 sessions at 4-week intervals for CaHA, 1 session HA	10% resorption at follow-up but patient remained satisfied	None	6 months

CaHA, Calcium hydroxylapatite; *ECDS*, en coup de sabre; *HA*, hyaluronic acid; *NR*, not reported; *PMMA*, polymethyl methacrylate; *PRS*, Parry–Romberg syndrome; *UVA*, ultraviolet A light phototherapy.

thickness.[65] Eventual material resorption limits long-term results to <2 years.[63] PLLA has been used in patients with PRS and facial linear scleroderma (LS)[65] with subjective improvement in aesthetic deficits (Table VII). Authors who used PLLA in patients with morphea and SSc noted that the tough, fibrosed skin created injection difficulties with the first 2 sessions, subsequently improving with following sessions, and limited injection volumes to 1 to 1.5 mL per session. PLLA has also been used as adjuvant treatment[66] combined with structural fat grafting[67] in patients with PRS as a skin-thickening agent before eventual fat transfer,[68] and for small volumetric deficits in a combined PLLA/fat transfer/IPL treatment regimen.[27]

Hyaluronic acid

Hyaluronic acid (HA) is a naturally occurring glycosaminoglycan found in tissue extracellular matrix that provides volumizing effects via keratinocyte proliferation, water binding,[63] and de novo type I collagen production.[69] These properties have made bacterial derived cross-linked HA fillers among the most widely used, with results persisting for as long as 18 months after 1 treatment.[70] Choksi et al[71] first reported on its use in a patient with ECDS to reduce enduring volume loss after the disease was made inactive by ultraviolet A1 light phototherapy. The authors made particular note of the financial constraints that will undoubtedly prevent many patients with morphea from pursuing reconstructive procedures but recommended large-particle HA fillers as an ideal option to maximize volume changes per amount of filler used (level of evidence III). Further studies also reported positive response to treatment of ECDS with HA filler, and specifically recommended the use of blunt-tipped cannulas to reduce trauma and prevent complications such as pain, bruising, swelling, or potential tissue necrosis caused by vascular damage.[72] In general, the technique to use blunt-tipped cannulas is similar among all patients. A thicker sharp cannula or needle is used to create an entry point for a thinner blunt-tipped cannula used for injection.[72] This technique can be enhanced with subcision and expansion of underlying tissue with normal saline to help prevent nodularity after the procedure. Although no cases of vascular compromise have been reported, some recommend injection volumes of 1 to 1.5 mL to prevent vascular compression leading to similar necrosis (level of evidence III).[65,72] We have used HA filler successfully to treat facial cosmetic deficits in a patient with bilateral PRS (Fig 3), for lip augmentation in patients with SSc and microstomia (Fig 4), and in patients with localized scleroderma on

Table X. Strength of recommendations for injectable treatment for morphea and systemic sclerosis

Recommendation	Recommendation no.	Level of evidence	Studies
When performing fat transfer for Parry—Romberg syndrome, more treatment sessions with greater overcorrection margins may be necessary	2.1	IIA	Slack et al[62]
Repeat fat injections can show improved survival compared with the initial graft and cumulative improvements in functional and patient-reported outcomes	2.2	III	Jiang et al[42] and Almadori et al[54]
The following injectable fillers can be used in patients with morphea and systemic sclerosis if disease is inactive and stable, without the need to restart disease-modifying medications			
Poly-L-lactic acid	2.3	III	Onesti et al,[27] Onesti et al,[65] Clauser et al,[66] and Grimaldi et al[68]
Calcium hydroxyapatite	2.4	III	Cox and Soderberg[77]
Polymethylmethacrylate	2.5	III	Franco et al[76]
Hyaluronic acid	2.6	III	Choski and Orringer,[71] Sivek and Emer,[72] Watchmaker,[73] Thareja et al,[119] and Arsiwala[120]
Large-particle hyaluronic acid filler can serve as an ideal option when financial constraints require maximum volume correction with minimal treatment	2.7	IV	Choski and Orringer[71]
The use of blunt-tipped cannulas can reduce trauma and prevent complications, such as pain, bruising, swelling, or potential tissue necrosis caused by vascular damage	2.8	III	Sivek and Emer[72]
For filler injection, injection volumes of 1-1.5 mL are recommended to prevent vascular compression and subsequent necrosis	2.9	III	Onesti et al[65] and Sivek and Emer[72]

Level IA evidence includes evidence from metaanalysis of randomized controlled trials; level IB evidence includes evidence from ≥1 randomized controlled trial; level IIA evidence includes evidence from ≥1 controlled study without randomization; level IIB evidence includes evidence from ≥1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

the face (ECDS) and truncal/extremity lesions.[73] Recently, a case of scleroderma-induced microstomia treated with serial hyaluronidase injections led to subjective improvement of mouth closure and eating.[74] The second article in this continuing medical education series includes more detailed information with regard to side effects and types of filler recommendations.

Calcium hydroxylapatite and polymethyl methacrylate

Calcium hydroxylapatite microspheres within carboxymethyl cellulose carrier gel serve as dermal filler that facilitates fibroblast growth. The volume-enhancing effects are evident at the time of treatment and persist for ≤18 months.[63] Polymethyl methacrylate microspheres dispersed in magnesium-carboxy-gluconate-hydrolactic gel is a permanent injectable filler option. Modern variations have improved consistency in electrostatic charge and particle shape and size that have improved long-term stability and biocompatibility.[75] Two case reports on the use of these filler types in patients with inactive morphea are summarized in Table IX.[76,77] We were unable to find any reported cases of methacrylate hypersensitivity among this population.

In summary, based on the available data, multiple modalities appear to be cosmetic injectable treatment options for patients with inactive disease (level of evidence III). Physicians should expect the initial injections to be difficult because of increased dermal resistance with improvement of resistance over subsequent sessions. This often requires the use of multiple needle changes during injections and the use of more volume than needed for patients without these autoimmune conditions. In addition, more volume for fat transfer than typically required and counseling of patients on the likelihood of multiple

Table XI. Surgical treatment options for Parry—Romberg syndrome and en coup de sabre scleroderma

Single surgical procedures	Facial reconstruction	Lipofilling[108]
		Polyethylene implants[121]
		Medpor implant[18]
		Cell-assisted lipotransfer
	Flaps and grafts	Myocutaneous flap[122]
		Omental flaps
		Free vascular parascapular graft[78]
		Thoracodorsal flaps
		Vascularized serratus anterior muscle flap
		Free groin flaps
		Composite galeal frontalis flap
		Perforator-based anterior muscle flap
	Volume restoration	Autologous fat transplantation[123]
		Fat transfer + modified Kligman formula[124]
	Tissue expansion	Soft tissue expansion + artificial bone graft[125]
	Acellular dermal matrices	AlloDerm tissue matrix[126]
Combined surgical procedures		
Cheek implants + fat grafts + platelet-rich plasma[48]		
Three −dimensional + free anterolateral thigh[127]		
Poly-L-lactic + lipofilling + intense pulsed light[27]		
Superficial temporal fascial flap + lipofilling		
Revascularized free flap + dermal graft		
Revascularized free flap + lipoinjection[78]		
Revascularized free flap + Medpor implant		
Revascularized free flap + genioplasty		
Revascularized free flap + liposuction		
Coleman lipoinjection + polyglactic acid		
Coleman lipoinjection + blood platelet gel		
Lipoinjection+ galeal flap + free dermal graft + bone and cartilage graft		

sessions are usually needed (level of evidence IIA). Treatment recommendations are summarized in Table X.

SURGICAL INTERVENTIONS

Key points

- Surgical procedures are often considered in patients with ECDS and PRS to improve volume, symmetry, and contour
- There are many techniques for facial reconstruction and often a combination of treatments and multidisciplinary care are required[78]

Surgical treatment options

Management of patients with morphea and SSc is mostly geared toward controlling the underlying inflammatory disease via a combination of topical agents, systemic therapies, and phototherapy.[79,80] Although these may be effective in mitigating disease progression, they do not address the resulting atrophy and dyspigmentation.[81] Surgical procedures are often considered in patients with ECDS and PRS to improve cosmetic appearance. While the timing of surgical treatment remains controversial,[78] there is often a delay until disease is inactive to reduce the risk of reactivation and multiple surgeries.[79,82-84] Many surgical modalities may be used in the treatment of ECDS and PRS, and it is important to preevaluate defect shape, size, and underlying bone deformity in order to choose the ideal surgical option for each individual. Table XI lists the surgical treatment options. Please see the second article in this continuing medical education series for the American College of Rheumatology (ACR) consensus guidelines for the perioperative management of patients with rheumatic diseases.

Dermal fat grafting. Dermal fat grafting techniques are usually indicated in patients with type 3 facial tissue atrophy, defined as thin soft tissue and bony structures, and type 4, characterized by severe facial depressions, where the skin is very close to bone.[85] The donor site is often the inguinal region and needs to be slightly larger than the defect size.[85] The reported complications are hematoma, undercorrection, edema, induration,[85] partial flap loss, and cellulitis.[78] An algorithm proposed by Lee et al[86] suggests that linear lesions <1 cm can be treated with resection and local flat or Z-plasty, and

oval/round lesions with length <5 cm, width <1 cm, and depth <2 cm are good candidates for free fat graft, dermal fat graft, or artificial dermis.[86] Dermal fat grafting seems to be an effective treatment for ECDS, with few complications and lasting results.[87,88] Dermal fat grafts can also be used in conjunction with porous polyethylene implants[89] (level of evidence III).

Bone and cartilage grafts. The use of bone and cartilage grafts to restore contour of the frontal bone are commonly indicated for patients with PRS with more severe defects in combination with soft tissue augmentation.[83,90] There are many techniques for facial reconstruction, and often a combination of treatments and a multidisciplinary team are required to treat facial tissue depressions.[83] Recently, a computer-assisted technique combining autologous outer cortex graft with fat grafting demonstrated good outcomes in patients with PRS.[91] Table XI details more surgical treatment options for PRS and ECDS.

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Answers to CME examination

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