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Connective Tissue Disorders and Cosmetical Procedures

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Abstract

Background: Cosmetical procedures like fillers can also aggravate more generalized skin conditions or connective tissue disease. Connective tissue disease has been reported to occur following cosmetic surgery with injection of the foreign substances paraffin and silicone. However, the vast majority of patients with connective tissue disorders have great concerns over changing facial features, and this worsens with age. Scleroderma en coup de sabre, morphea, discoid lupus erythematosus lesions are disfiguring diseases for which only limited therapeutic options exist for cutaneous complications. Fillers, botulinum toxins, autologous fat transplantation and lasers were succesfully used to correct the atrophic and scatricial defects during inactive period of connective tissue disorders. Cosmetic correction of stable connective tissue disorders using several techniques has been variably effective in isolated case reports and small case series. The score systems are used to measure connective tissue disorders activity. The evaluation of serum levels of acute phase reactants may be a sensitive marker of connective tissue disease activity which may be helpful in maintaining or withdrawing cosmetical procedures in patients with connective tissue disorders.

Introduction

There has been much debate about whether or not cosmetical procedures such as fillers, lasers, PRP can actually cause an connective tissue diseases including scleroderma, lupus erythematosus, dermatomyositis, morphea. Although the theory has gained the attention of the U.S. Food and Drug Administration (FDA), at this time, there is not enough information to accurately determine whether or not injecting cosmetic material like fillers and lasers into a person with a low or compromised immun system can lead to an autoi mmune connective tissue diseases. But permanent fillers like silicone should be absolutely avoided, since connective tissue disease has been reported to occur following cosmetic surgery with injection of the foreign substances paraffin and silicone. However indication for fillers include scleroderma and lipoatrophy or depressed scars of connective tissue diseases. Fillers, botulinum toxins, autologous fat transplantation and lasers were succesfully used to correct the atrophic and scatricial defects during inactive period of connective tissue disorders. Cosmetic correction of stable connective tissue disorders using several techniques has been variably effective in isolated case reports and small case series. The score systems are used to measure connective tissue disorders activity. The evaluation of serum levels of acute phase reactants may be a sensitive marker of con-

nective tissue disease activity which may be helpful in maintaining or withdrawing cosmetical procedures in patients with connective tissue disorders. Connective tissue diseases characterized by inflammation of tissues are caused by autoantibodies that the body incorrectly makes against its own tissues. These conditions are called autoimmune diseases. Included in this category are the following conditions, which are often handled by a dermatologist: Dermatomyositis, scleroderma (morphea), lupus erythematosis. In this review, we evaluate cosmetical procedures of connective tissue diseases with skin involvement [**1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25**].

Connective tissue diseases such as scleroderma, progressive systemic sclerosis (PSS), rheumatoid arthritis, systemic lupus erythematosus, polymyositis have been reported to occur following cosmetic surgery with injection of the foreign substances paraffin and s ilicone (human adjuvant disease). The occurrence of PSS is approximately threefold greater than expected for all women believed to have undergone such surgery, and PSS developed primarily in individuals injected with paraffin. Prolonged exposure to the injected substance may play a role in the induction of these immunologic disorders. They subsequently develop both clinical and serologic manifestations of connective tissue disease. In some instances, remission of the disease has followed removal of the injected substance. The role of the injected material in the induction of the disease remains uncertain. In most western countries paraffin injection was not popular because of its potential adverse effects, including pulmonary emboli and local irritation. *Van Nunen* et al. reported three patients in Australia with this disease who had received breast augmentation with silicone gel-filled, elastomer envelope-type prostheses. The patients were diagnosed as having SLE, MCTD, and RA with Sjogren's syndrome. Drug-induced lupus erythematosus can also be regarded as an adjuvant d isease in some respects. Unfortunately, precise denominator data are not available to a scertain whether patients undergoing implantation surgery are at increased risk of developing connective tissue disease. Patients with infections such as sinusitis, periodontal disease, ear, nose, or throat infections, or dental abscesses should not be treated until the condition has resolved. Increasingly, clinical evidence is emerging indicating that these infections might subsequently invade implanted filler areas, inducing biofilm reactions. Later, transition from infection to an established hypersensitivity, via toll-like receptors, is possible, since these molecules have been shown to be involved in the development of many pathological conditions like autoimmune connective tissue diseases. De rmal filler treatment can also aggravate connective tissue disease, or might not be suitable in some of these conditions including active chronic discoid lupus erythematosus or lupus erythematosus, active but not end-stage scleroderma, mixed connective tissue disease. Dermal fillers are not contraindicated in patients in whom wound healing is normal, even though they may have an underlying systemic disease. No association has been established between use of fillers an d autoimmune conditions. Thus, patients with lupus or scleroderma who have normal wound healing may be treated. Although bruising tends to occur more extensively with certain injection techniques, such as fast injection, aggressive fanning, high-volume filler deposits, or large bolus injections (more than 0.5 mL per bolus), all sensible precautions should be taken with any injection technique [**1,2**].

Timing of other cosmetic procedures: Botulinum toxin treatment should be planned two weeks prior to filler. Using botulinum toxin first can help in assessment of the need for treatment of residual issues such as static lines and deep folds that can be treated with hyaluronic acid fillers. From a safety perspective, however, the treatments may be given on the same day. Microdermabrasion, chemical peels, and intense pulsed light should ideally be carried out 1–2 weeks pre- or posttreatment and fractional resurfacing 3–4 weeks distant to allow erythema to diminish and the skin barrier to reestablish. One small pilot study, however, compared injection of hyaluronic acid-based filler immediately followed by laser, radiofrequency (RF), or pulsed light treatments (IPL) to injection of filler alone. The results suggested that laser, RF, and IPL may be safely administered immediately after hyaluronic acid gel implantation. Data sug-

gest that deeper filling immediately before laser therapy, when the concomitant swelling may facilitate the effect of the laser, may be acceptable. Patients with a history of dental or facial surgery may have areas of unusual vascular distribution because of aberrant neovascularization after the trauma of a procedure in combination with a decrease in tissue laxity. It is of paramount importance that any material placed under the skin is injected under sterile conditions using aseptic technique. The patient's skin should be cleaned, degreased, and disinfected. There are no universally recommended topical antiseptics, but chlorhexidine, chloxylenol, iodophors, alcohol, and iodine may all be appropriate. Rarely, a patient may experience an allergic reaction to cleansers and topical anesthetic agents, and physicians need to recognize the signs and immediately remove the product responsible from the skin. Patients may also be allergic to the lidocaine mixed in the syringe of the filler. The injector should wash his/her hands thoroughly, remove watches and rings, and wear surgical gloves (although not necessarily sterile). Areas of irritation or inflammation should not be injected, needles or cannulas must be sterile and changed frequently during the procedure, excess filler on the syringe needle should only be removed with sterile gauze, and aseptic technique followed throughout the procedure. Treatment areas should not be reinjected within two weeks of the initial procedure. Even with pe rfect tissue integration, a certain level of edema and extravasation of blood can be present in the early postinjection phase, creating an ideal environment for bacteria to proliferate upon repeated injection. Before injecting, aspiration should be performed as a prophylactic measure, particularly in highly vascularized areas, and a new needle without filler used prior to deep bolus injections. Blood on aspiration indicates that the needle is in a blood vessel and the injection point should be altered. Injection must be performed slowly and with caution, allowing time to assess and react to any untoward response, changes in skin color, or disproportionate pain. Filler should be injected slowly with a low flow rate in small quantities at multiple points and overfilling avoided. Small-bore needles are recommended by some to slow the injection rate and blunt needles/cannulas in high-risk regions to reduce vessel injury. Avoiding anesthesia with epinephrine (adrenalin) close to a vascular bundle to prevent vasospasm and tenting the skin to avoid the vascular supply are also appropriate recommendations. To prevent the technique-related problems of irregularities, lumps, or beading, injection technique and depth should be appropriate for the area being injected and the area massaged after injection. Accidental intramuscular injection of synthetic fillers other than hyaluronic acid and collagen should be avoided, since muscle contraction can dislocate the filler and create unwanted lumps. Once a hypersensitivity reaction is suspected, the time of onset should be established, the patient's medical history re-reviewed, and a full medical examination undertaken. In cases of diagnostic uncertainty, special investigations include blood tests such as markers for inflammation (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]) and acute-phase reactants. The latter appear to be the most sensitive markers for the prese nce of autoimmune/inflammatory syndrome induced by adjuvants (ASIA) related to dermal filler use. A biopsy (if a previously used product is of unknown type), MRI, or ultrasound (high frequency) should be considered[**1**].

A study of responses to a wide range of dermal fillers demonstrated that calcium hydroxyapatite, methacrylate, acrylamides, and silicone produced notable chronic activation of the immune system (mediated by macrophages and polymorphonuclear leukocytes). By contrast, hyaluronic acid elicited little immune response. The plasma levels of myel operoxidase and the chitin-like proteins chitotriosidase and YKL-40 may be important markers indicative of immune response activation in certain cases. The primary diagnostic symptoms of infection are erythema, warmth, tenderness, pain, swelling (usually at or close to site of injection), local signs of abscess (pustules, nodules, areas of fluctuation, crusts), and systemic fever. It is prudent to be highly suspicious of any area near the site of injection exhibiting local symptoms. Differentiation between infection and hypersensitivity is important during diagnosis, as the use of steroids should be avoided in i nfection. Important differentiating factors which indicate infection are skin temperature, pain (absent, more diffuse, or less intense in cases of hypersensitivity), fever or

signs of an abscess, and the absence of pruritus. The time of injection in relation to time of onset, blood tests, or infective markers (such as CRP, ESR, and procalcitonin) may be diagnostically useful, and purulent material may be cultured to determine the type of pathogen and the most appropriate antibiotic. Acute, mild infections can be treated with oral antibiotics. Empiric treatment should begin with macrolide or tetracycline antibiotics, which may have some anti-inflamm atory and immunomodulatory effects in cosmetical procedures of patients with CTDs. Two-drug therapy should be considered to broaden the spectrum of cover such as ciprofloxacin 500–750 mg bid for 2–4 weeks, clarithromycin 500 mg + moxifloxacin 400 mg bid for 10 days. Delayed-onset nodules may also result from the incorrect use of fibroblast stimulatory fillers (eg, polylactic acid, calcium hydroxyapatite) in areas where skin is thin or mobile. Foreign body granulomas may form as the body's immune system responds to a foreign body that cannot be broken down by the usual mechanisms. They can develop several months, or even years, after injection and present as red, firm papules, nodules, or plaques. Diagnosis of nodules and lumps is further complicated by the fact that clinicians are sometimes faced with patients with unknown or incomplete medical and cosmetic treatment history. Hypersensitivity-related nodules may be treated with antihistamines (eg, cetirizine, loratidine), oral steroids (eg, medium-dose pulse therapy prednisolone, 60 mg/day), methyl prednisolone (eg, a total of 240 mg in six weekly decreasing doses), and/or nonsteroidal anti-inflammatory drugs once infection has been ruled out. RF or infrared energy may also be a useful adjunctive treatment option in some areas. For late-onset nodules or granulomas, intralesional steroids (betameth asone 5 mg/mL or triamcinolone 10–40 mg/mL for 10 days up to 4 weeks) can be considered, although care needs to be taken to avoid skin atrophy. For persistent cases, additional measures can include a series of injections of 5-fluorouracil (50 mg/mL) in combination with steroids and/or lidocaine (1:3), methotrexate, local tacrolimus, cortivasol, allopurinol, colchicine, isotretinoin, imiquinod, laser-assisted removal, or ultimately excision by surgery as a last resort [**1**].

Systemic Sclerosis (Scleroderma, Morphea)

HIt is characterized by induration of the skin and systemic organ involvement. The etiology is unknown and the pathogenic steps leading to fibrosis and sclerosis remain unclear. The key pathogenic events of systemic sclerosis are generally thought to be endothelial cell damage and excessive deposition of collagen and other matrix proteins into tissue. There is evidence that certain cytokines, such as transforming growth factor-β (TGF-β) and connective tissue growth factor, might play a role in the accumulation of collagen in the skin and internal organs. Clinically, the disease is characterized by the common occu rrence of Raynaud's phenomenon and esophageal involvement. Other organ systems that are commonly involved, particularly in the diffuse form of scleroderma, are the lung, the heart, and the kidney. Diagnosis is based on clinical findings and specific abnormalities in laboratory test results. Although scleroderma is not uniformly fatal, certainly it is an incapacitating disease leading to severe complications. It is therefore not surprising that the focus in the treatment of this disease is on preventing complications and prolonging the life span of severely affected individuals. However, scleroderma is also associated with a disturbing disfigurement of facial features and expression. Most obvious to the patient and others is the characteristic loss of facial expression, retraction and thinning of lips, microstomia, and radial furrows around the mouth. The vast of majority of the scleroderma patients are deeply concerned about their facial features. Some studies have indicated that patients with scleroderma have significant physical disability as well as feelings of isolation. A study conducted in 1996 determined the prevalence of depressive symptoms among patients with systemic sclerosis. That study found that 48% of the patients evaluated had mild de pressive symptoms and an additional 17% had moderate to severe depressive symptom s. The investigators also found that younger patients and those diagnosed with systemic sclerosis at younger ages had more severe cognitive-depressive symptoms.Inadequate social support systems contributed to greater depressive symptoms [**3**].

En coup de sabre is a localized variant of scleroderma that presents as a linear, atrophic depression affecting the frontoparietal aspect of the face and scalp. Occasionally, involv ement of underlying structures, including muscle, bone, and rarely meninges and brain, occurs resulting in medical morbidities for the patient. Given that this variant occurs on the face, however, it is often the cosmetic aspect for which patients seek out care and intervention. Indeed, the disfigurement and both its psychological and social effects may have a significantly negative impact on the patient's quality of life. Unfortunately, treatment for active en coup de sabre is difficult, and for stable lesions, attempts at improving cosmesis have led to suboptimal results. Surgical excision, autologous fat grafting, autologous bone grafting, and placement of synthetic tissue inserts have been performed with varying degrees of success. Dermal filler treatments offer an attractive option as they are much less invasive and possess distinct advantages compared to the aforementioned techniques. Hyaluronic acid filler is particularly well suited for soft tissue augmentation because of its tolerability, availability, relatively low cost, reversibility,and efficacy in volumization. There are two cases in which hyaluronic acid filler is utilized in the correction of hemifacial atrophy seen in Parry–Romberg syndrome, a distinct but related variant of linear scleroderma. These were both in combination with other modalities: in one case autologous fat transfer and in the other, calcium hydroxylapatite filler. Specifically in regard to en coup de sabre, there is a case report of hyaluronic acid filler used in conjunction with AlloDerm tissue matrix, which is essentially cadaveric dermis. *Thareja* et al. reported a novel case of en coup de sabre in which hyaluronic acid filler alone was successfully used to correct the atrophic defect. The en coup de sabre variant of linear morphea presents as an atrophic linear streak that is most often located on the paramedian forehead and scalp. While single lesions are most common, multiple lesions may coexist in a single patient, with reports suggesting that the lesions may follow Blaschko's lines. The lesions commence as contractions and firmness of the skin over the affected area. This is followed by the development of an ivory-colored, irregularly shaped, sclerotic plaque, which often has hyperpigmentation at the periphery. Finally, profound atrophic changes may be noted leading to a permanent, depressed defect. The length of the active, inflammatory stage typically ranges from 2 to 5 years. Attempts at halting the progression during this phase have led to the use of a variety of pharmacologic therapies, including topical, intralesional, or systemic glucocorticoids, antimalarials, retinoids, penicillamine, penicillins, phenytoin, griseofulvin, calcitriol, interferon, and methotrexate. Other modalities such as phototherapy and physiotherapy have also been employed. Although several regimens have shown benefit in case series, no controlled trials have been performed. Cosmetic correction of stable en coup de sabre using several techniques has been variably effective in isolated case reports and small case series. The use of hyaluronic acid filler as monotherapy in patients with en coup de sabre has been reported only twice. In addition, hyaluronic acid fillers have been used as an adjunct to concomitantly used implants or other types of filler in cases of linear scleroderma of the face as follows. A case of Parry–Romberg syndrome, a variant of localized scleroderma characterized by facial hemiatrophy treated with calcium hydroxylapatite filler, has been reported by Cox and Soderberg. Their approach was modeled after a recent prospective study of 30 patients by Caruthers and Caruthers that outlined the benefits of calcium hydroxylapatite injections for HIV-associated facial lipoatrophy. Cox and Soderberg report using five injections of calcium hydroxylapatite at approximately four weeks intervals. The patient also received a single injection of hyaluronic acid in an attempt to correct volume depletion. Significant improvement in volume depletion was noted and the patient was very satisfied with the r esult. In a recent report by *Lane* et al. upper lip injections of hyaluronic acid filler wer e given to a patient with Parry–Romberg syndrome. This filler improved cosmetic a ppearance and was used before a planned autologous fat transfer. Finally, the use of hyaluronic acid filler as an adjunctive agent has been reported in a patient with en coup de sabre who received a synthetic tissue implant with AlloDerm. In this case, *Robitschek* et al. used hyaluronic acid filler to smooth out the borders of the implant and create a more even forehead contour. In terms of the cosmetic correction of atrophic skin lesions, hyal uronic acid offers many advantages. Hyaluronic

acid is the most prominent glycosaminoglycan in the skin. When injected into the skin, it volumizes, softens, and hydrates the skin by potently binding to water. In addition to these benefits, it plays a role in cell growth, membrane receptor function, and adhesion. It has also been shown to stimulate collagen production, which may explain why some patients, in our experience, with injectable hy aluronan appear to have some permanent improvement after multiple treatments. While typically used for the improvement of age-related changes, it may also be used off label on a compassionate basis for the benefit of patients such as ours who suffer from atrophy as a sequela of a disease process. It must be noted, however, that in some areas of en coup de sabre lesions, the skin may be somewhat tethered to underlying structures. For these particularly bound down areas, filler alone will not suffice to correct the defect, and more invasive procedures may be required. The cosmetic improvement is nonetheless substantial. Ongoing injections will be required to maintain the cosmetic outcome, which may indeed improve with repeated treatment. Hyaluronic acid filler may be safely and succes sfully used as monotherapy for temporary cosmetic improvement of en coup de sabre lesions. The benefit is most prominent in well-selected patients who may experience atrophy but in whom the prominent feature is not tethering to underlying structures [**4, 5, 6, 7, 8**]. Scleroderma en coup de sabre is a disfiguring disease for which only limited therapeutic options exist. Three cases of facial linear scler oderma treated with autologous fat transplantation with acceptable results are presented. Autologous fat transplantation was preferred to corrective surgery because of the extent of the lesions and absence of any associated facial distortion. Fat as a filler was chosen to reduce the risk of adverse effects. Adipocytes are suggested to have wider biological effects than other fillers and may offer more durable results. At least two transplantations were needed to evoke a significant effect [**6,7**]. The scleroderma en coup de sabre is a variant of localized scleroderma that occurs preferentially in children. The disease progresses with a proliferative and inflammatory phase and later atrophy and residual deformity, which are treated with surgical techniques such as injectable fillers, transplanted or autologous fat grafting and resection of the lesion. Among the most widely used fillers is hyaluronic acid. However, there are limitations that motivate the search for alternatives, such as polymethylmethacrylate, a permanent filler that is biocompatible, nontoxic, non-mutagenic and immunologically inert. A case of scleroderma en coup de sabre in a 17-year-old patient, who was treated with polymethylmethacrylate with excellent aesthetic results, was reported [**8**]. In the phase of residual atrophy and deformity, the treatment of choice is done with surgical techniques such as injectable fillers, transplanted or autologous fat grafting and resection of the lesion. Among the fillers, the most widely used is the hyaluronic acid, a hygroscopic, absorbable gel. However, limitations like durability and cost of the filler are factors that lead to the search for other alternatives. *Franco* et al. reported a case of scleroderma en coup de sabre treated with polymethylmethacrylate (PMMA), with the objective of illustrating a little-used option [**6**]. There are some surgical therapeutic options for the treatment of residual atrophy. Among them are injectabl e fillers (hyaluronic acid, PMMA, calcium hydroxylapatite), transplanted or autologous fat grafting and resection of the lesion. It is important to emphasize that injectable fillers should only be used when the skin lesion is stable, that is, without growth or alterations in consistency or skin color. However, the patient should be warned that the treatment does not prevent from a possible relapse to the proliferative phase, since disease activity lasts around three to five years and may extend up to 25 years, with an uncertain progression time. PMMA is a permanent filler, biocompatible, not toxic, non-mutagenic and immunologically inert. PMMA does not require a previous cutaneous test as its microspheres are 100% polymerized. Therefore, allergies are rare. They used it in 10% and 30% concentrations. Besides these advantages, one of the factors that made us choose the product was its ready availability at our service, since the patient did not have the means to purchase the medication. After a PMMA application, there is a reaction of foreign body type that induces the onset of giant cells that wrap each particle of the product, leading to new collagen and blood vessels formation. That means that the defect is corrected by the volume of the product added and the incorporation of cells and collagen fibers

that appear at the site. According to the instructions accompanying the product, PMMA is recommended for facial and body volume correction and also to correct lipodistrophy caused by use of antiretrovirals in patients with HIV. Its use has also been reported for treatment of facial lipoatrophy induced by cutaneous lupus panniculitis. PMMA filling is a good therapeutic option for esthetic improvement of residual scarring following scleroderma and an alternative to avoid more invasive surgical procedures[**6**]. If the lesion is narrow, it can be resected and directly sutured; in the case of a wide lesion, many different reconstructive techniques, directed at augmentation of deficient soft tissue volume, have been proposed such as autologous tissue grafts, biomaterials, pedicled flaps, and free flaps. Adipose-derived regenerative cells (ADRCs) can be easily processed from lipoaspirated fat and can provide a significant quantity of multipotent cells for a variety of therapeutic regenerative medicine therapies. There is an increasing interest in a possible therapeutic role of ADRCs from processed lipoaspirate for many applications, including their use as soft-tissue fillers. *Karaaltin* et al. reported the application of a successful ADRC therapy for a linear scleroderma en coup de sabre deformity [**7**].

Virzi et al. indicated a report of combined platelet-rich plasma and lipofilling treatment provides great improvement in facial skin-induced lesion regeneration for scleroderma p atients. The use of stem cells, including mesenchymal stem cells (MSCs), for regenerative medicine is gaining interest for the clinical benefits so far obtained in patients. *Virzi* et al. investigated the use of adipose autologous tissue in combination with platelet-rich plasma (PRP) to improve the clinical outcome of patients affected by systemic sclerosis (SSc). Ad ipose-derived mesenchymal stem cells (AD-MSCs) and PRPs were purified from healthy donors and SSc patients. The multilineage differentiation potential of AD-MSCs and their genotypic-phenotypic features were investigated. A cytokine production profile was evaluated on AD-MSCs and PRPs from both healthy subjects and SSc patients. The adipose tissue-derived cell fraction, the so-called stromal vascular fraction (SVF), was coinjected with PRP in the perioral area of SSc patients. Histopathological and phenotypical analysis of adipose tissue from SSc patients revealed a disorganization of its distinct architecture coupled with an altered cell composition. Although AD-MSCs derived from SSc patients showed high multipotency, they failed to sustain a terminally differentiated progeny. Furthermore, SVFs derived from SSc patients differed from healthy donors in their MSC-like traits coupled with an aberrant cytokine production profile. Finally, the administration of PRP in combination with autologous SVF improved buccal's rhyme, skin elasticity and vascularization for all of the SSc patients enrolled in this study. This innovative regener ative therapy could be exploited for the treatment of chronic connective tissue diseases, including SSc. Recent findings have shown that adipose tissue is an important source of MSCs. Therefore, this prompted great interest in the scientific community, leading to the discovery of advanced techniques used for the collection and isolation of MSCs from lipoaspirates and their use in the clinic. Lipofilling is a surgical protocol that was standardized by Dr Sidney Coleman in 1997, aiming at the transfer of autologous adipose tissue. The current lipofilling technique consists of three phases: subcutaneous tumescent liposuction from the abdomen, medial knee, or trochanter regions; centrifugation of the lipoaspirate sample to remove blood elements and the oil fraction from adipose components; and autologous injection of “purified” adipose tissue. Adipose tissue is composed of mature adipocytes, fibroblasts, adipose-derived mesenchymal stem cells (AD-MSCs), immune system cells, and endothelial cells, which are grouped as the stromal vascular fraction (SVF). The presence of all these cellular elements, in particular the large number of AD-MSCs, makes the SVF the most prominent candidate for lipofilling therapeutic success. In fact, AD-MSCs secrete high levels of growth factors and cytokines such as vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF), which are all crucial molecules for lipotransfer engraftment and tissue regeneration. AD-MSCs are endowed with great multilineage differentiation potential and relevant regenerative properties. AD-MSCs are able to grow in suspension as sph eroids without serum and they can be identified through a high expression level of the CD271 marker. The most affected districts in SSc patients are the joints of distal limbs and perioral and malar areas. A gradual reduction

was observed in the opening and extension rates of the labialis rhyme, due to fibrosis and loss of endothelium integrity, inflammatory mononuclear infiltrate, and high production of reactive oxygen species (ROS). These conditions promote a compensatory VEGF overproduction by the endothelium. In healthy subjects the increase of VEGF is coupled with platelet-derived growth factor (PDGF), endothelin-1 (ET-1), transforming growth factor beta (TGF-β), connective tissue growth factor (CTGF), and monocyte chemoattractant protein-1 (MCP-1) production, thus promoting angiogenesis. SSc patients show a high production of VEGF, which is not however fol lowed by an improvement of endothelial capillarity, giving rise to telangiectasia. Being that a single lipofilling treatment usually is not sufficient in order to obtain efficient regeneration in SSc patients, a combination of autologous tissue together with an abundant cytokine source would be preferable. Platelet-rich plasma (PRP) consists of a gel fraction obtained from peripheral blood. PRP contains a high number of platelets, cytokines, and growth factors. Different studies have shown that PRP promotes coagulation and wound healing, exerting an antiphlogistic effect on the acceptor site and hence stimulating rapid tissue regeneration. Several studies have demonstrated that PRP has a beneficial impact on the regenerative potential of MSCs, and that the combined use of PRPs and lipoaspirates increases graft survival while mainta ining the plumping effect in breast reconstruction. The injection of autologous adipose ti ssue-derived SVF, enriched in MSCs, in combination with PRP, into the perioral and malar areas of SSc patients not only improved the facial morphofunctional issues, but significantly enhanced the buccal's rhyme, skin elasticity, and vascularization. The use of MSCs has been introduced relatively recently in the clinical practice of regenerative medicine. Several studies highlighted their self-renewal, multilineage differentiation capacity, and immunomodulatory properties. As well as being multipotent stem cells, the MSCs are able to differentiate into different cell types including adipocyte, chondrocyte, osteoblast, and neuron-like cells. Among their properties, their accessibility and easy expansion suggest that use of MSCs may be a useful therapeutic approach for several disorders. Nowadays adipose tissue is considered an innovative source of MSCs suitable for cell-based therapy. Autologous micrografting of AD-MSCs was recently demonstrated to induce positive effects on SSc patients. *Griffin* et al. recently established that AD-MSCs from healthy individuals and SSc subjects present the same phenotype and differentiation capacity, while migration and proliferation are impaired. Notably, significant difference in the SVF composition characterized the adipose tissue obtained from SSc patients as compared to that from healthy subjects. The adipose compartment of SSc patients showed a disruption of its peculiar morphology and a bare presence of mesenchymal cells, thus suggesting that the inflammatory microenvironment, typical of this systemic disease, could affect the architecture and the adipose cell reservoir. Indeed, the abnormal presence of proinflammatory cytokines in the adipose tissue compartment of SSc patients impaired the differentiation and maturation of MSCs toward the adipose phenotype. Accordingly, mesenchymal stem cell-like traits of MSCs purified from SSc patients significantly differed from those of healthy subjects. Although both AD-MSCs derived from healthy and SSc SVFs contained a subpopulation positive for CD271, a putative adipose stem cell marker, the SSc ADMSCs lacked the ability to differentiate into functional mesenchymal cellular types. Cells within the SVF in SSc patients, according to their MSC-related gene profile and proliferation rate, are likely to be in a late stage of commitment, which impairs the ultimate phase of cell differentiation. Several transcription factors are known to play a crucial role in the last steps of differentiation, thus regulating cell maturation of AD-MSCs in adipocytes, osteocytes, or chondrocytes, such as CCAAT/enhancer-binding protein alpha (CEBPα), runt-related transcription factor 2 (RUNX2), or SOX-9, respectively. Likewise, the failure of AD-MSCs from SSc patients in functional differentiation could also depend on a delayed maturation block due to a dysregulation at the transcriptional level. Vascular damage and alteration of subcutaneous microcirculation caused by angiogenic factor deficiency are described to be among the major clinical signs of SSc patients. The SSc SVF compartment defected in the production of several master regulators of angiogenesis, which is crucial for both engraftment and tissue regeneration. Despite

the significant advances in the therapeutic options for the treatment of SSc patients, the novel pharmacological compounds that target the hypoxia signaling pathways and immune response have not yet proven beneficial to quality of life. These evidence supports the hypothesis that coinjection of autologous SVF and PRP in SSc patients could provide the correct balance of angiogenic and growth factors to improve tissue regeneration, thus representing an optimal combinatorial therapy against SSc [**14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24**].

Belgaumkar et al. reported a case of en coup de sabre treated with platelet-rich plasma. Contour defects such as linear morphea are difficult to treat and can be a cause for great cosmetic and sociopsychological morbidit y. The pivotal discovery of platelet-derived growth factors in promoting wound healing, angiogenesis, and tissue remodeling has paved the way for various uses of platelet-ric h plasma (PRP). A remarkable reduction i n hyperpigmentation of overlying skin was noted which further enhanced the cosmetic outcome. The effect was sustained until the end of follow-up period of 6 months after the last PRP sitting. No secondary changes or side effects were noted during the entire course of treatment. PRP therapy could be safe and effective in the treatment of linear morphea over face and scalp as demonstrated in this case [**25**]. Although the use of PRP as an adjuvant to other natural and synthetic fillers has been reported in previous studies, PRP use as monotherapy in morphea so far is hitherto unr eported. Although monotherapy of small contour defects with autologous PRP requires more number of sittings as compared to its use in adjunction with fillers and fat grafts, it can produce similar long-term results. PRP monotherapy required a total of 12 weekly sittings and is currently on maintenance "touch up" injections of PRP every six months. In comparison, dermal fillers are far more costly than PRP. They too may require repeated sessions depending upon the type of filler used (the cost of treatment being approximately proportional to the life of the filler). Hence, in a resource-limited setting or patients with limited affordability, PRP monotherapy is a cost effective substitute especially for those who cannot afford dermal fillers or the procedural cost of fat or dermal grafts. The advantages of using PRP alone as against its combination with fat/dermal grafts are its simplicity, minimal cost, and low-risk potential of the procedure[**25**]. PRP also has a mit ogenic effect on endothelium and other mesenchymal stem cells such as adipocytes and dermal fibroblasts. This stimulatory effect of platelets on collagen remodeling and fibroblasts warrants its use in the correction of small contour defects. *Bendinelli* et al. have reported anti-inflammatory effect by reduction of COX 2 and CXCR4 gene expression. All these mechanisms explain the efficacy of PRP in indications such as acne, scars, chronic ulcers, and alopecia and as a corollary, disfiguring contour defects such as morphea [**26**]. *Jin* et al. demonstrated the increased survival of fat grafts and fillers when harvested in freshly prepared autologous PRP [**27**]. Ortega and Sastoque successfully used bovine tendon coll agen, glycosaminoglycans, and fat grafts harvested in PRP to correct contour defects in Parry Romberg syndrome [**28**]. An open issue in localized scleroderma concerns the surgical treatment of facial deformities. In the past, this treatment approach has been highly debated, considering both conservative therapy and orthopedic–orthodontic or maxillofacial ones. A recent study on a case series of 17 patients with JLS of the face (Parry–Romberg syndrome or scleroderma en coupe de sabre) confirmed the potential usefulness of the surgical treatment, mainly including fat injections, bone paste cranioplasty and Medpor implants. All individuals, evaluated by a multidimensional questionnaire on the psychos ocial effects of the surgical interventions, supported the benefits of this treatment, would consider repeated surgery and recommend surgery to other patients with en coupe de sabre and Parry Romberg syndrome. Unfortunately, the timing on when these procedures should be performed and how to establish complete disease remission to avoid unpleasant side-effects are still unclear [**28,29**].

Rimoin et al. reported An improvement of “En Coup de Sabre” morphea and associated headaches with Botulinum toxin injections. The mechanism by which botulinum toxin improved both of these symptoms is unclear. It can postulated that its mechanism of reducing morphea associated headache are similar to its effects on other types of headaches, although it has never been reported as a treatment

for morphea-associated headaches. Perhaps, the sclerosis of the morphea plaque causes tightening and spasm of surrounding muscles by disrupting normal musculocutaneous architecture, and botulinum toxin helps relax these tense muscles by blocking the release of acetylcholine. Several recent studies have suggested that botulinum toxin reduces different types of neuropathic pain, such as postherpetic neuralgia and trigeminal neuralgia, through a different mechanism. Animal studies show that botulinum toxin inhibits the release of neuropeptides such as substance P and glutamate, which are involved in the regulation of pain and inflammation. As such, it may be botulinum toxin's effect on several neurotransmitters, not just acetylcholine, that resulted in pain relief for this patient with morphea. Although the pathogenesis of the atrophy of coup de sabre is un known, one possible mechanism is neuralbased vasoconstriction causing atrophy of skin, muscle, periosteum, and bone. By blocking the transmission of norepinephrine, botulinum toxin prevents- the signal that causes vasoconstriction in vascular smooth muscle, leading to subsequent vasodilation, which is its basis for helping in Raynaud phenomenon. Thus, the cosmetic improvement with OnabotulinumtoxinA could be secondary to therapeutic denervation [**30**]. *Mousty* et al. reported a case of Botulinum toxin type A for treatment of dyspareunia caused by localized scleroderma. A total of 50U of BoNT/A was injected into the affected side (right puborectalis, right pubococcygeus and perineal body muscles). BoNT/A is a selective neuromuscular blocking agent. When injected for therapeutic purposes, it binds to peripheral nerve terminals and prevents the release of acetylcholine into the synaptic cleft, leading to muscle paralysis. In this patient, dyspareunia was caused by both levator ani muscle spasm and skin atrophy related to menopause and scleroderma [**31**]. Successful treatment of the muscle spasm with BoNTA allowed recovery of sexual life [**31**].

Le at al reported a case of thoracic outlet syndrome secondary to localized scleroderma treated with botulinum toxin injection. The main lesson of this case is that presumed deep tissue fibrosis of localized scleroderma can impinge on the brachial plexus and subclavian vessels, causing TOS. In addition, it d emonstrates that botulinum toxin injection can provide dramatic relief, allowing avoidance of invasive surgery in TOS secondary to localized scleroderma. TOS results from compression of the neurovascular structures traversing the thoracocervical region. Neurologic complications are commonly seen in patients with localized scleroderma, particularly with the linear subtype involving the face an d head, which is referred to as "en coup de sabre." However, these complications, manifesting as seizures, focal neurologic deficits, and migraines, have a different mechanism whereby the symptoms are a result of direct involvement of the neurologic structures. The symptoms of the patients are more consistent with an entrapment neuropathy, wherein the tissue fibrosis affects the area surrounding the neurovascular bundle. There have been only a few reported cases of neuropathies caused by compression due to collagen deposition of localized scleroderma, such as carpal tunnel syndrome, dystonia, and hemimasticatory spasm [**32**].

BoNT/A injection was reported in one case of localized scleroderma associated with facial hemiatrophy, with the product injected into the facial masseter muscle. The involuntary spasms and pain caused by localized scleroderma were improved by this procedure. *Kim* et al. successfully treated hemimasticatory spasm of a localized scleroderma patient wit h local botulinum injection of the masseter muscle. The extracutaneous manifestations of localized scleroderma are mostly associated with the linear subtype, where there is involvement of the deeper underlying structures. *Kim* et al. reported a case of hemimasticatory spasm (HMS) associated with localized scleroderma and facial hemiatrophy with elec trophysiological data to delineate the underlying pathophysiological mechanism. Local injection of botulinum toxin A into the masseter muscle resolved the patient's symptoms. Although a few patients have been helped by carbamazepine or phenytoin therapy, treatment with oral drugs has been of no benefit in most patients with HMS. Local injection of botulinum toxin A into affected muscles may be the treatment of choice in HMS [**33**].

The main hesitation in treating patients with scleroderma is the perceived risk of poor wound healing following many surgical and laser procedures. However, there is no evidence that patients with scleroderma heal po-

orly. Various treatment modalities such as the carbon dioxide laser, fillers, botulinum toxins have been used for correcting the facial disfigurements afflicting patients with scleroderma. Carbon dioxide laser resurfacing is traditionally reserved for patients with severe rhytids, photoaging and improvement of acne scars. It has not traditionally been used for severe rhytidosis in systemic sclerosis patients. Perhaps this is because of the concern over laser wounding of the skin and the subsequent healing capacity in scleroderma patients. The results showed significant clinical improvement in the facial appearance of all patients with scleroderma treated with the CO2 laser with complete re-epithelialization by 7–10 days. There were no reported complications and no recurrence of rhytids over a 12–18 month observation period. There have also been reports on the successful use of the pulsed dye laser for the treatment of mat-like facial telangiectasias in scleroderma patients. These studies indicate that healing appears adequate and the results encouraging in this group of patients with systemic sclerosis. Management with lasers is obviously not the only treatment option available for improving the facial appearance in scleroderma patients. There are a number of studies detailing other treatment modalities for enhancing the facial appearance in scleroderma patients including fat transfer and soft tissue augmentation. This area needs to be further investigated as good to excellent cosmetic results can be obtained with many of the modalities3,8. Laser devices are increasingly being used for the treatment of dermatologic conditions, including but not limited to acne and acne scarring, vascular lesions, pigmented lesions, hair and tattoo removal, scar revision, photodamage, and skin rejuvenation. As advances in technology continue to emerge, it is likely that treatments incorporating laser will be employed for an ever-expanding number of skin diseases. Connective tissue diseases (CTD) are medically challenging and often treatment-r esistant conditions, and the use of laser therapy in these conditions remains controversial. The clinical manifestations of several CTD including lupus erythematosus (LE), morphea, scleroderma, and dermatomyositis will be reviewed. The evidence presented in the literature as it currently exists for the use of lasers in the treatment of these entities will also be discussed, with a focus on efficacy and complications. Monochromatic excimer laser has been reported to contribute to marked improvement whilst confronting localized scleroderma. To sum up, the 308-nm excimer laser should be considered a valuable treatment option when challenging diverse skin disorders both in terms of efficacy and safety; however larger investigations with long-term follow-up need to be conducted in order to thoroughly corroborate its use [**29**]. Scleroderma encompasses systemic and localized sclerosis, or morphea. Eleven studies using laser therapy for various forms of morphea or systemic sclerosis were identified in the literature. Four studies discussed the use of PDL, the largest of which was a case series of eight individuals with morphea and associated facial telangiectasias. The authors reported that telangiectasias were successfully treated without recurrence from 6 months to 2 years after treatment. The remaining reports noted varying results in patients with en coup de sabre or plaque morphea. The formation of telangiectasias is inherent to the disease process in morphea and scleroderma and may recur. The formation of new telangiectasias is to be expected, especially in individuals in whom the underlying condition is not well controlled. Therefore, clinicians should expect the treatment of telangiectasias a ssociated with these CTD to involve recalcitrance and recurrence. IPL was used to treat microstomia in four patients with systemic sclerosis, with softening of the skin and an increase in oral aperture in three of the four patients. Four case reports of the use of ablative and fractional ablative CO2 lasers demonstrated successful treatment of contractures, rhytides, and calcinosis of the digits in a total of 11 patients with morphea. Fractional ablative CO2 laser was successfully used in the treatment of morphea-related joint contracture across the ankle, limiting plantar flexion. The patient reported subjective improvement in range of motion almost immediately after the single treatment session. At 4-month and 1-year follow up visits after the single treatment, she had regained and maintained full plantar flexion with softening of the contracture on palpation without any adverse effects, suggesting that fractional laser therapy may be associated with a good safety profile in the treatment of morphea. In a report using the 308-nm excimer laser, improvement in the texture and pigmentation of individual pla-

ques of morphea of five individuals was achieved. Severe Raynaud's disease with chronic finger tip ulceration in a patient with scleroderma was successfully treated using the 1064-nm neodymium-doped YAG laser (1,064-nm), with improved mobility and circulation and ultimate healing of ulcerations. Processes inherent to the pathogenesis of sclerodermaand morphea at the molecular level may be relevant to healing and ultimate cosmetic result after laser therapy. Morphea and scleroderma are characterized by a profibrotic state, driven by cytokines including interleukin 4 and 6 and transforming growth factor beta. There is also microvascular disease, with injury to the vascular endoth elium and perivascular inflammation, increased dermal microvascular pericytes, and re plication of the vasculature basement membrane. These processes of microvascular disease and profibrosis, in addition to other factors, may contribute to the presence of poor wound healing in patients with scleroderma and morphea. Precautions should be taken in patients with sclerosis in treatment with laser therapy, especially when using ablative or resurfacing lasers, in which wound healing will be a more prominent factor. Fractional ablative lasers have been used in patients with limited systemic sclerosis without report of problem with wound healing, but this remains an important consideration before undertaking ablative laser treatment. Theoretically, fractional resurfacing lasers may lessen the likelihood of impaired wound healing after therapy because they produce isolated columns of injury rather than broad, uninterrupted areas of injury [**2,21**].

Rosholm et al. analysed the effects of intense pulsed light in microstomia in patients with systemic sclerosis. The effects of intense pulsed light (IPL) on collagen structures are well known in the treatment of photodamaged skin. The objective of this study was to investigate the effect of IPL on sclerotic skin by treating patients with microstomia due to systemic sclerosis. 13 patients all with microstomia and systemic sclerosis were treated with IPL, PR (530-750 nm filter) and/or VL (555-950 nm filter) applicator. They were treated in the perioral area 8 times with 3-4 weeks of interval and follow-up for 6 months. The outcomes were the inter-incisal distance and the inter-ridge distance. A significant increase in mouth opening of 4.1 mm (95% confidence interval, 1726-6638, $p < 0.005$) was found in the inter-ridge distance when comparing the distance before treatment with the distance at six-month follow-up. No significant difference was found in the inter-incisal distance. The patients experienced improved mobility and better control of lip movements after the treatments. IPL can improve the inter-ridge distance between the lips in patients with microstomia due to systemic sclerosis but does not affect the inter-incisal distance, which is also dependent on the mobility of the mandibular joints. This treatment can be considered an adjunctive therapy in patients with microstomia due to systemic sclerosis [**34**].

Shalaby et al. studied the effect of fractional carbon dioxide laser versus low-dose UVA-1 phototherapy for treatment of localized scleroderma. Fractional ablative laser resurfacing has been used effectively in scar treatment via abnormal collagen degradation and induction of healthy collagen synthesis. Therefore, fractional ablative laser can provide an effective modality in treatment of morphea. The study aimed at evaluating the efficacy of fractional carbon dioxide laser as a new modality for the treatment of localized scleroderma and to compare its results with the well-established method of UVA-1 phototherapy. Seventeen patients with plaque and linear morphea were included in this parallel intra-individual comparative randomized controlled clinical trial. Each with two comparable morphea lesions that were randomly assigned to either 30 sessions of low-dose (30 J/cm2) UVA-1 photo therapy (340-400 nm) or 3 sessions of fractional CO2 laser (10,600 nm-power 25 W). The response to therapy was then evaluated clinically and histopathologically via valid ated scoring systems. Immunohistochemical analysis of TGF-ß1 and MMP1 was done. Patient satisfaction was also assessed. Wilcoxon signed rank test for paired (matched) samples and Spearman rank correlation equation were used as indicated. Comparing the two groups, there was an obvious improvement with fractional CO2 laser that was superior to that of low-dose UVA-1 phototherapy. Statistically, there was a significant difference in the clinical scores, collagen homogenization scores, and patient satisfaction scores. They concluded that fractional carbon dioxide laser could

be a promising treatment modality for cases of localized morphea, with proved efficacy of this treatment on clinical and histopathological levels[**35**].

Dinsdale et al. evaluated a comparison of intense pulsed light and laser treatment of t elangiectases in patients with systemic sclerosis. Cutaneous telangiectases are a chara cteristic and psychologically distressing feature of SSc. Their aim was to assess the efficacy of two light-based treatments: pulsed dye laser (PDL) and intense pulsed light (IPL). Nineteen patients with facial or upper limb telangiectases underwent three treatments with PDL and IPL (randomly assigned to left- and right-sided lesions). Outcome measures were clinical photography (assessed by two clinicians), dermoscopy (assessed by two obse rvers), laser Doppler imaging (LDI) and observer and patient opinion, including patient self-assessment psychological questionnaire s [Hospital Anxiety and Depression Scale (HADS), Adapted Satisfaction with Appearance Scale (ASWAP)]. Comparison between 16-week follow-up and baseline photography scores (from -2 to +2 on a Likert scale, with >0 being improvement) were a mean score for PDL of 1.7 (95% CI 1.4, 2.0) and for IPL 1.4 (0.9, 1.8), with a mean difference between PDL and IPL of -0.3 (-0.5, -0.1) (P = 0.01). Dermoscopy scores also improved with both therapies: PDL 1.3 (1.1, 1.5) and IPL 0.8 (0.5, 1.1), again greater with PDL (P = 0.01). LDI showed decreases in blood flow at 16 weeks, indicating a response to both therapies. All patients reported benefit from treatment (more preferred PDL at 16 weeks). Psychological questionnaires also indicated improvement after therapy with mean change in ASWAP of -13.9 (95% CI -20.5, -7.4). No side effects were reported for IPL; PDL caused transient bruising in most cases. Both PDL and IPL are effective treatments for SSc-related telangiectases. Outcome measures indicate that PDL has better outcomes in terms of appearance, although IPL had fewer side effects [**36**].

Hanson et al. reported a case of linear scleroderma in an adolescent woman treated with methotrexate and excimer laser. The lesion decreased in size considerably with relief of symptomatic discomfort by 7 months. The excimer laser has been reported to effectively treat a variety of dermatologic conditions, including morphea. Its mechanism of action may be via depletion of T cells, altering apoptosis-mediating molecules and decreasing cytokine expression. This patient had a good clinical response with a combination of these two modalities. The epidermal perforation with transepidermal elimination of calcified necrotic collagen is a unique complication that may have been secondary to this combination treatment modality [**37**].

Tawfik et al. reported pulsed dye laser in the treatment of localized scleroderma and its effects on CD34+ and factor XIIIa+ cells. A de creased number of CD34+ cells and an increased number of Factor XIIIa+ cells are seen in the affected skin of morphea. The flashlamp pulsed dye laser (FLPDL) has been used in the treatment of localized morphea with promising results. The purpose of this study was to evaluate the therapeutic effectiveness of the pulsed dye laser in localized scleroderma and to assess its effect on CD34+ cells, Factor XIIIa+ cells, and blood vessels. Thirty patients with plaque morphea were treated with a FLPDL (585 nm wavelength, 450 µs pulse duration). Fluence ranged from 7.5 to 8.5 J/cm(2). Sessions were performed biweekly for a maximum of 6 months. Patients showed varying degrees of improvement of indurated skin. There was no worsening or further improvement at the treated sites during the follow-up assessments at 3, 6, and 12 months. An increased number of CD34+ cells were found in both the upper and the lower dermis, and a decreased number of Factor XIIIa+ cells were found in the lower dermis. The FLPDL could be effective in the treatment of morphea, as confirmed by the changes in the pathologic tissue and levels of CD34+ and Factor XIIIa+ cells [**38**].

Kineston et al. reported the use of a fractional ablative 10.6-µm carbon dioxide laser in the treatment of a morphea-related contracture [**39**].

Digital ulcers are difficult to heal, increasing the chance of infection, gangrene, amputation and limited functional use of hands. They are a complication in scleroderma or systematic sclerosis (SSc) and occur in approximately 50% of patients. Low level laser therapy, iontophoresis and ultrasound can facilitate the healing of chronic digital ulcers in patients with scleroderma. Lord and Obagi reported a case of Scleroderma and Raynaud's phenomenon improved with high-peak power laser

therapy. Potobiotherapy is the clinical application of light for healing decubitus ulcers and other superficial wounds. Mester and colleagues, who reported healing of chronic soft tissue ulcers with application of a low-energy (1–4 J/cm2) ruby laser introduced low-level laser therapy (LLLT) as a therapeutic modality. They studied more than 1,000 human cases of recalcitrant ulcers of different etiology and reported improvement in more than 70% of those cases using various laser systems with a dose of approximately 4 J/cm2. Subsequent studies have followed, studying LLLT in Raynaud's phenomenon and diabetic microangiopathy. A case report by Eisen and Alster demonstrated marked softening of a sclerotic morphea plaque and improvement in skin coloration with the use of a 585-nm pulsed dye laser without side effects or complications. In a study of LLLT using an 890-nm diode laser by Ezzati and colleagues, irradiation of third-degree burns on rats demonstrated greater wound closure rate. This case report supports the use of a novel laser not previously reported in the treatment of systemic sclerosis and Raynaud's phenomenon. Studies have demonstrated that LLLT from the visible red spectrum accelerates cell growth in a cellular model of wound healing and improves cellular metabolism in a dose- and time-dependent manner. The use of near-infrared light (NIR) may have significant advantages over visible red light for clinical applications. The longer wavelength of NIR light minimizes scatter produced by superficial layers of the skin and allows for penetration of the light into deeper layers of skin that are most active during wound-healing processes. In addition, NIR produces heating of deeper skin layers, promoting greater blood flow and further accel erating the healing process. In a wound-healing study using a scratched monolayer of fibroblasts as a wound model and a 980-nm diode laser as a light source, Skopin and Molitor demonstrated that overexposure negates the beneficial effects of laser exposure. Fibroblasts demonstrated peak growth rates at moderate laser exposure intensities and insignificant growth rates at higher exposure intensities and doses than the control group that was not exposed to laser. The use of laser therapy on diabetic wounds is also promising. In a study of three-times-per-week laser therapy using a 532, 633, 810, 980, and 10,600-nm laser or polychromatic light-emitting diodes (LEDs) in the treatment of diabetic wounds and burns in mice, Al-Watban demonstrated that the 633-nm laser was the best light source for all wound and burn models. In this induced diabetes model (diabetes induced with streptozocin), wound and burn healing were improved 40.3% and 45%, respectively with the 633-nm laser. The LED devices were also efficacious in healing diabetic wounds. In this case, the authors used a 1,064-nm laser with a fluence ranging between 10 and 15 J/cm2 and a pulse width of 0.30 ms delivered at 10 Hz. This treatment modality is defined as high-peak power laser therapy. This is a case of successfully treated scleroderma and Raynaud's phenomenon in a patient who did not respond to multiple systemic medications and sympathectomy. High-peak power laser therapy is a promising treatment for patients who have failed conventional therapies. Furthermore, the 1,064-nm Nd: YAG laser at the aforementioned settings is safe in all skin types. African-Americans have been reported to have a higher incidence of scleroderma (22.5 cases per million per year) than Caucasian women (12.8 cases per million per year) and African-American women are reported to have more-severe disease. Reveille and colleagues demonstrated in a prospective cohort that Hispanics and African-Americans were more likely than whites to have diffuse skin involvement and digital ulcerations, making high-peak power laser therapy a promising therapeutic option for this subset of patients as well. Although various laser modalities have demonstrated eff icacy and safety in treating scleroderma, Raynaud's phenomenon, and morphea, the me chanism of action is unknown. One mechanism by which LLLT might stimulate the wound-healing process is light energy absorbed by mitochondria, which increases cell energy and stimulates the release of chemical mediators. Schindl and colleagues postulated that temperature elevations during laser therapy might be related to a release of cytokines that might improve and treat diabetic microangiopathy. Studies have shown that LLLT a ffects the cellular components of wound healing by modulating the proliferation of ma crophages, lymphocytes, fibroblasts, endothelial cells, and keratinocytes. It also i nfluences microcirculation, cellular respiration, and adenosine triphosphate synthesis, the release

of granulocyte-monocyte colony-stimulating factor and other cytokines, transformation of fibroblasts into myofibroblasts, and collagen synthesis. LLLT speeds up wound healing by modulating the inflammatory response, fibroblast proliferation, angiogenesis, collagen deposition, and re-epithelialization, although it is yet to be determined whether laser therapy results in the downregulation of certain genetic markers associated with systemic sclerosis. Further studies are needed to better elucidate the mechanism of action of lasers in these disorders [**40**].

Both ablative and non-ablative fractional lasers have been applied to various uncommon hair disorders. The purpose of this study was to demonstrate the clinical effects of fractional laser therapy on the course of primary follicular and perifollicular pathologies and subsequent hair regrowth. A retrospective review of 17 patients with uncommon hair disorders – including secondary cicatricial alopecias was conducted. All patients had been treated with non-ablative and/or ablative fractional laser therapies. The mean clinical improvement score in these 17 patients was 2.2, while the mean patient satisfaction score was 2.5. Of the 17 subjects, 12 (70.6%) demonstrated a clinical response to non-ablative and/or ablative fractional laser treatments, including secondary cicatricial alopecia (scleroderma). These findings demonstrated that the use of non-ablative and/or ablative fractional lasers promoted hair growth in certain cases of uncommon hair disorders secondary scleroderma without any remarkable side effects. NAFL has also been shown to be effective in the treatment of alopecia areata, male pattern hair loss, and female pattern hair loss, with several murine studies suggesting that low-fluence and high-density NAFL irradiation affects the hair cycle by promoting telogen to anagen transitions. Accordingly, it has now been suggested that laser therapy-associated hair regrowth may result from Wnt 5a and β-catenin expression. For all AFL treatment sessions, a laser fluence of 30 to 50 mJ was delivered to the affected areas in static operating mode without local anesthesia using a density of 150 spots/cm2 (spot diameter of 120 μm; percent coverage of 8.1% – 10.2%). For patients treated with AFL, an antibiotic ointment containing mupirocin was also applied to all the affected areas. In patients with scleroderma-induced secondary cicatricial alopecia (cases 10 and 11), improvement of depressed sclerotic scars on the frontal scalp was observed after the first AFL treatment session. Furthermore, terminal hair regrowth was also noted on the depressed alopecic patches in two patients treated with AFL. *Cho* et al. used AFL to treat sclerotic lesions on the scalp that had resulted from various primary pathologies. After several AFL treatment sessions, these lesions improved both in texture and in overall degree of induration, with terminal hair regrowth additionally observed. However, the mechanism of hair recovery as a result of this treatment remains to be elucidated. *Cho* et al. attributed the therapeutic effects of AFL and NAFL to physical breakage and thermal stimulation of the lesions, which may serve to induce regeneration and realignment of the thick collagen bundles in the scar tissue responsible for the resulting alopecic patches. As AFL has been shown to induce immediate tissue tightening (vs. NAFL), reduction in the width of the atrophic patches may also have contributed to the clinical improvement observed. In a previous study, *Ito* et al. demonstrated Wnt-dependent de novo hair follicle neogenesis in adult mouse skin after wounding, specifically showing that a wound stimulus is sufficient to trigger the regeneration of hair follicles from epithelial cells by inducing an embryonic phenotype in the skin. The wounds resulting from fractional laser therapy may have contributed to hair follicle neogenesis. These findings demonstrate that the use of AFL and/or NAFL promoted hair growth in certain cases of uncommon hair disorders secondary scleroderma without any remarkable side effects [**41**].

Kim et al. reported a case of en coup de sabre presenting as a port-wine stain initially treated with a pulsed dye laser. Vascular erythematous stains can sometimes precede the onset of definite sclerosis. In a case series of linear morphea, patients were misdiagnosed as having skin infection, nevus or salmon patch with a mean diagnostic delay of 3.9 years [**42**].

Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune connective tissued is ease. SLE can affect numerous organ systems with cutaneous manifestation in more than

half of individuals. Cutaneous lupus erythematosus (CLE) can also occur in isolation. Its manifestations are morphologically diverse and can be characterized as acute, subacute, or chronic. All subtypes of CLE may be evaluated according to the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), a tool developed and validated to score CLE on the basis of disease activity (the presence of erythema, scale, and hypertrophy) as well as damage (dyspigmentation, scarring, atrophy, and panniculitis). Discoid lupus erythematosus (DLE) is a chronic CLE characterized by coin-shaped (or discoid) plaques well demarcated by inflammatory hyperpigmentation. Lesions eventually lead to permanent and disfiguring scarring and skin atrophy. DLE lesions develop in approximately 6–10% of individuals with SLE. Due to its scarring nature, prompt diagnosis and treatment of DLE is critical. Diagnosis is made based on clinical findings as described, most often above the neck and in some cases on mucosal surfaces. Hyperpigmentation and scale extend into dilated hair follicles, causing follicular plugging. Skin atrophy, scarring, and scarring alopecia may result and can seriously impact quality of life. In some cases biopsy will be performed which demonstrates characteristic changes of basement membrane thickening, follicular plugging, increased mucin and a superficial and deep perivascular lymphocytic inflammation with adnexal involvement. Current first-line treatment for DLE consists of photoprotection in conjunction with topical or oral corticosteroids, topical calcineurin inhibitors, and systemic antimalarial therapy. When DLE is refractory to these measures, other agents with varying degrees of proven efficacy are used. Currently, no medications have been approved specifically, and many of the drugs described in the literature were developed for use in other autoimmune disorders. The association between tobacco and DLE is controversial. One study reported a higher prevalence of smoking in individuals with DLE compared to controls. Additional studies have shown higher CLASI disease severity scores in current smokers with worse quality of life, suggesting an increase in disease activity. Current smokers also had a higher prevalence of combination antimalarial therapy, indicating escalation of therapy. Moreover, studies demonstrate a statistically significant decrease in efficacy of antimalarial medication in individuals who have currently or ever smoked, as determined by CLASI score and clinical assessment. While a causative mechanism of tobacco on the develo pment or progression of DLE remains incompletely understood, cessation of smoking is strongly r ecommended. The most-recent proposed criteria from the Systemic Lupus International Collaborating Clinics include 11 clinical and immunologic criteria. SLE may affect the integument in several ways, and a cutaneous predominance is reflected, with four of the 11 clinical criteria involving skin manifestations (acute cutaneous lupus, chronic cutaneous lupus, oral and nasal ulcers, and nonscarring alopecia). Acute cutaneous LE (ACLE) is characterized by erythematous, edematous lesions without scale, including the classic malar or butterfly rash over the base of the nose and malar eminences sparing the nasolabial folds. Other l esions of ACLE include a morbilliform eruption, photosensitive eruption, bullous lupus, and the toxic epidermal necrolytic variant of SLE. Subacute cutaneous LE (SCLE) is classically characterized by symmetric, photodistributed erythematous papules and annular plaques or psoriatic-like plaques with scale. The lesions most commonly occur on the extensor surfaces of the arms, the neck the shoulders, and the upper chest. Telangiectasias and dyspigmentation may persist upon resolution of lesions of SCLE. Chronic cutaneous LE (CCLE) includes discoid LE (DLE), chilblain LE, tumid LE, and lupus panniculitis. DLE is the most commonly encountered form of CCLE and is characterized initially by erythematous, indurated plaques with adherent scale that progress to peripheral hyperpi gmentation, central hypopigmentation, a trophy, and scarring. The lesions are commonly found on the head and neck, including involvement of the conchal bowls and the scalp, resulting in permanent cicatricial alopecia. DLE may have a favorable prognosis, with 5–10% of patients who present with lesions limited to DLE progressing to systemic i nvolvement of lupus. Chilblain LE is characterized by lesions on acral surfaces commonly precipitated by exposure to cold temperatures or a damp climate. The lesions are erythematous to purple patches or plaques occurring on the fingers, toes, or face (nose). Tumid LE (LE tumidus) is characterized by edematous, indurated plaques reminiscent of urticaria on

the face or trunk. Lupus panniculitis presents as mobile, often nontender subcutaneous nodules located on the buttocks, proximal arms, or face. Lupus profundus is characterized by lesions of tumid LE with overlying changes of DLE [**43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55**].

Lupus erythematosus panniculitis (LEP) is an inflammatory disease of the subcutaneous tissue, which can occur with or without systemic lupus erythematosus. Lesions often resolve with prominent atrophy, and there is a paucity of data regarding effective treatments. The use of polymethylmethacrylate, a permanent dermal filler, has been reported. Alth ough nonpermanent fillers, including hyaluronic acid (HA) and poly-L-lactic acid (PLLA), have been used successfully for atrophy associated with linear morphea and progressive hemifacial atrophy, there are no reports of nonpermanent fillers for LEP-induced atrophy. *Eastham* et al. presented the first case of LEP-induced facial atrophy successfully treated with PLLA and HA. Various treatments have been used to inhibit the inflammatory phase of LEP. However, disfigurement is frequently observed after the inflammation resolves. They used PLLA and HA for effective soft-tissue augmentation of extensive LEP-induced facial atrophy. Concern exists regarding the use of dermal fillers in the setting of connective-tissue disease, given the theoretical risk of connective-tissue disease reactiv ation as a result of antigenic stimulation. Reactivation or stimulation of connective-tissue disease has not, however, been reported with purified, inert fillers, including PLLA and HA. They presented the first case of LEP-induced facial atrophy successfully treated with PLLA and HA. These agents should be considered potential therapeutic options for minimally invasive correction of LEP-induced facial atrophy, if injected in the context of quiescent LEP. They proposed that MRI could be helpful to exclude subclinical inflammation. Additional data are necessary to fully elucidate both the role of MRI in assessing subclinical disease activity and the safety and efficacy of the use of dermal filling agents in patients with LEP [**43**].

Bhari et al. reported a case of a 22-year-old woman with lipoatrophy treated successfully with polyacrylamide hydrogel injectable filler. This led to an effective, long-lasting restor ation of subcutaneous volume loss. Lupus panniculitis, a form of chronic cutaneous lupus, is a rare inflammatory disease in which the predominant lymphocytic infiltrate is seen deep in the lower dermis and subcutaneous tissue. It primarily affects the head, upper arms, trunk, and thighs, and presents as firm, sharply defined, tender nodules from 1 to several centimeters in diameter. The overlying skin becomes attached to the subcutaneous nodules and is drawn inward to produce deep, saucerized depressions. Approximately 50% of patients with lupus panniculitis have evidence of systemic lupus, but the systemic features in these patients tend to be less severe. The resultant aesthetic defects are a major concern for most of the p atients. Polyacrylamide hydrogel is an intradermal, permanent and non-biodegradable filler. Injectable waterbased polyacrylamide gel contains a small percentage of polyacrylamide (2.5% in Aquamid) with the remaining portion being water. After injection, polyacrylamide particles become enmeshed into the local fibrous matrix and as a result, rarely migrate away from the treated area. It is a non-biodegradable permanent filler; thus, successful well-placed augmentation may last without re-treatment or with minor touch-ups for a long period. The common reported side effects are hypersensitivity reactions, local infection, injection-related adverse effects, hematoma, ecchymosis, granuloma formation, migration of the filler, and rarely thromboembolism. In a double-blind, randomized, multicenter trial of 315 subjects treated with polyacrylamide hydrogel, 1 serious infection was seen on 12-month follow-up which resolved within 5 days after appropriate treatment. In a cross-sectional study of 751 HIV-infected patients to evaluate the 10-year safety of polyacrylamide hydrogel in the management of facial lipoatrophy, indurations were detected in 6.7% ofpatients, nodules in 3.8%, and 5 (4.8%) patients had a local infection. Rare reported side effects are foreign body granuloma and thromboembolism. Delayed gel induration, one of the major complications of polyacrylamide filler which generally occurs between 10 and 28 months after treatment, even after 9-years of follow-up. Polyacrylamide hydrogel dermal filler can be considered as a relatively economical therapeutic option to correct the large subcutaneous defects in

selected cases of lipoatrophy secondary to lupus panniculitis[**56**].

Lipodystrophy disorders are a group of heterogeneous conditions connected with defective metabolism and progressive loss of fat that affects the subcutaneous tissue of the face, upper limbs, thoracic region, occasionally extending to the groins or thighs, and rarely visceral compartment. Multiple genetic forms are often associated with other metabolic and systemic anomalies, and result in a gradually progressive lipoatrophy accompanied by redistribution of the fat especially in the upper body. Acquired types can be related to various autoimmune disorders, like lupus erythematosus. Scarring and lipoatrophy e xposed on the face can be a psychological problem. The cheeks, zygomatic areas and nasolabial folds are the most common sites treated surgically where a limited functional restoration and good aesthetic results can be obtained. Improvement in the case of small facial contour deformities can be achieved with autogenic fat grafts or lipodermal grafts. Fat grafts transferred by lipoinjection are subject to resorption processes, similarly to surgical grafts. The limitation of this popular technique is the volume of the injected fat, as excessive fat transfer may jeopardize revascularization. However, the procedure can be r epeated multiple times and donor site morbidity is minimal. Grafts supplementation with adipose-derived stem/stromal cells (CAL technique) may prove superior to the facial recontouring technique employed in patients with lupus profundus. In some cases, dermal fillers like hyaluronic acid may be helpful in scar depression correction. Major areas of the resected necrotic skin together with the soft tissue defect may require coverage with either local or microvascular free tissue transfer. Different methods of local plasty can be indicated depending on the size and location of the lesion. Scalp defects can also be reconstructed with the use of expanders or the technique called “Nordström Suture”. Unlike fat grafting, the free flaps transferred for facial contour reconstruction provide large volumes of reliable tissue. Lipodystrophies are a wide group of diseases with various etiology, mainly genetic, metabolic or autoimmune. The treatment of this disease is chronic and not always effective. Proper diagnosis and adequate drug administration are of fundamental importance. Major concerns for patients with lipodystrophies are also aesthetic defects. That is why for such patients, apart from general treatment, possibilities to eliminate the cosmetic malformations are also important. Correction procedures are performed mainly on the exposed body parts – face, neck and upper limbs. There are many surgical methods to improve the patient’s appearance and the choice of technique depends on the severity of the process and the preference of the surgical center. One of the possibilities is to correct face or neck contours using the autologous fat. Pinski and Roenigk showed the results of surgical treatment in a group of 43 patients. All patients underwent autologous fat transplantation and indications included mainly lupus erythematosus. Authors concluded that autologous fat transplantation is a safe and effective procedure, with long follow-up observations (mean 26 months). *Yoon* et al. suggested that the autologous fat transfer is a good choice to correct face atrophic lesions in patients with lupus erythematosus. Patients with lipodystrophies, independently of the disease cause, may require aesthetic surgical procedures to improve their appearance. The plan of surgical treatment should be individual and depends on the localization and extension of lipoatrophy. In patients with lupus erythematosus autologous fat graft in the face area seems to be a safe and effective method of refilling the volume of atrophic tissues. It is worth emphasizing that the process of fat graft resorption is typical and placing autologous fat in the atrophic area does not accelerate the fat resorption. The state of tissue hypercorrection allows for achieving more lasting and satisfactory surgical effects. In patients with scalp scars, the effective method of their removal and hairline restoring is the usage of the tissue expander.

Physical modalities: Light, laser, and cryotherapies have all been reported in the treatment of lesions of DLE. Cryosurgery is a mainstay of dermatology but is reported in a single case study of hypertrophic DLE. Liquid nitrogen treatment 3–4 times at 4–6 week intervals resulted in softening of lesions with reduced erythema and pruritus and cosmetic improvement. Cryosurgery is itself associated with the risk of hypopigmentation and scar formation if lesions are frozen too deeply and thus is not routinely used in the treatment of DLE. Laser therapy has been reported effective in treating lesions of LE including DLE.

As recently summarized, the most data exists for pulsed dye laser (PDL) with a wavelength of 585–595 nm, reported in eight studies to result in clinical improvement. In one prospective study, 12 individuals with DLE were treated with PDL (585 nm, fluence 5.5 J/cm2, 0.45 ms, 7 mm spot) every 6 weeks for three sessions. At 6 weeks, 12 weeks, and 18 weeks, a statistically significant decline in CLASI measures of active disease was seen, with no significant change in the measures of damage, suggesting laser therapy may be more effective early in the course of disease. Side effects of pulsed laser therapy may include localized hypopigmentation, transitory hyperpigmentation, and slight scarring. Of note, existing evidence, including a review of 14 studies, reports no occurrence of disease flare in response to laser treatment. In summary, limited data suggests it may provide a safe and effective treatment option. Therapeutic success has been reported with laser and cryotherapy in patients with CLE. Although the use of argon and carbon dioxide lasers has been documented in a handful of case reports, several case studies support the effectiveness of pulsed-dye laser (PDL) therapy. The effectiveness of PDL is attributed to the selective destruction of blood vessels within the skin followed by inflammatory modulation and disease regression. Side effects of PDL are limited to localized hypopigmentation, transitory hyperpigmentation, and slight scarring. In a 1999 study, a clearance rate of 70 percent was observed in nine patients with DLE following treatment with PDL. Two patients developed transient hyperpigmentation as a result of therapy. Another series of 12 patients with recalcitrant DLE demonstrated a significant reduction in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score following three PDL treatments. A recent, prospective, open-label study achieved a clearance rate of more than 60 percent in 14 patients with different types of CLE. Clinical analysis demonstrated improvement in telangiectatic, erythema, and scaling components, but none in atrophy, hyperkeratosis, scarring, and pigmentation. Histopathological evaluation revealed a marked decrease in dermal lymphocytic infiltrate and basal damage. These studies collectively show PDL is an effective treatment of CLE, especially in patients with chronic DLE. However, when considering any physical treatment for CLE, a risk-benefit analysis is necessary due to the well-documented risk of inducing lesions with physical or laser treatments in CLE via the Koebner phenomenon [**57, 58, 59, 60, 61, 62, 63**].

Fourteen published studies and case reports have detailed the efficacy of laser treatment for various forms of cutaneous LE. The pulsed dye laser (PDL), with a wavelength of 585–595 nm, has been used in eight studies, including two prospective studies, of 31 cumulative patients. In two of these studies, 12 of 19 patients experienced complete resolution of their cutaneous disease (including tumid LE, SCLE, and DLE), with marked reduction in clinical skin scores, including size, erythema, and edema. No complications were noted. In the third prospective study, including 12 patients with DLE, PDL resulted in a statistically significant decrease in the Cutaneous Lupus Erythematosus Disease Area and Severity Index from a mean of 4.4 to a mean of 1.3 after three treatment sessions.6 Other case series and case reports detailing the use of PDL for cutaneous LE reported successful responses, and the majority of cases had no recurrence over follow-up times of 1–10 months. PDL was associated with transient hyperpigmentation in six patients, permanent pigmentation changes in one patient, and slight scarring in one patient. There were no complications in any other patients (n = 55). Raulin and colleagues have discussed the efficacy of PDL in the treatment of cutaneous lesions of LE and documented their experience of successful treatment of LE with PDL in more than 50 patients. The authors acknowledge the lack of use and reporting of lasers in treatment of LE and that laser medicine is not considered in treatment algorithms despite evidence to support that it is well tolerated and effective. Reasons that Raulin and colleagues proposed for PDL not reaching mainstream therapy for cutaneous LE include lack of awareness or interest on the part of dermatologists with little knowledge or experience with lasers or that those with the experience have a greater interest in the treatment of cosmetic and aesthetic concerns. Continuous-wave lasers, although no longer routinely used as first-line laser therapy for most cosmetic and medical indications, have been shown to result in successful treatment in patients with cutaneous LE. Two studies used the 488/514-nm argon laser in six patients with DLE and achieved complete

resolution in two and 60–70% improvement in another two. Slight scarring was noted in one patient. The fully ablative carbon dioxide (CO2) laser, with a wavelength of 10,600 nm, has been reported in two isolated case reports to be successful in improvement of the scarring lesions of DLE, with prolonged remission (1–2 years without recurrence). Fully ablative yttrium aluminum garnet (YAG) lasers have also been used in DLE, with two case reports demonstrating significant cosmetic improvement without adverse effects and 1–2 years without recurrence. There have been numerous reports of the use of lasers with wavelengths in the visible light spectrum (PDL, argon, and intense pulsed light (IPL) with a 515-nm filter). Adverse events after laser treatment of cutaneous LE have been reported, specifically with CO2 lasers, argon lasers, and PDL. Several of these were reported in the 1980s and 1990s, with technology, parameters, and techniques that have since become outdated and probably do not reflect current use of generally longer pulse durations and lower fluence settings. Skin fragility remains a concern in this patient population, and there have been reports of blistering and hypopigmentation after laser therapy for port wine stain in patients with SLE. Proposed mechanisms include antibody deposition in nonlesional skin, which primes the skin for a blistering response or other adverse effect. Traditional, fully ablative lasers used in previous reports probably had a greater risk for complications given the fragile nature of the skin in these patients, and the newer fractional ablative and nonablative devices are likely to have a lower side effect profile when used appropriately [**63**].

Recent studies reported that several treatments, including pulsed dye laser, CO2 laser, intense pulsed light (IPL), and 1,064-nm long-pulse neodymium-doped yttrium aluminum (Nd:YAG) have been used for the cosmetic treatment of DLE. *Byun* et al. reported a case of a DLE scar that was successfully treated with a combination therapy of IPL and Q-switched 1,064-nm Nd:YAG laser [**10**].

The treatment of cutaneous lupus erythematosus (CLE) with dye and argon laser has been evaluated in a number of articles in recent years. The improvement of telangiectasias and chronic erythema of the cutaneous lesions was based on the selective photothermolysis ablation of the dilated capillaries and venules. *Baniandres* et al. described the results of the treatment of cutaneous lesions of 14 patients; 8 with DLE and 6 with SLE. Three patients received a treatment with flashlamp pulsed dye laser (FPDL) (585 nm, 450 microseconds) with fluences in the range from 5 to 7.75 J/cm(2); the other 11 patients were treated with long pulsed dye laser (LPDL) (595 nm, 1.5-10 milliseconds) with fluences in the range from 6 to 13 J/cm(2) depending on the pulse duration. During a median follow-up of 10 months, they observed an average improvement in over 60% of the lesions. A few side effects were observed in all patients: four had transient hyperpigmentation and one patient had light scarring. Three patients had a relapse after more than 1 year; they were then offered conventional treatment. They confirmed that pulsed dye laser could a good alternative treatment for the erythema in active cutaneous lesions of lupus erythematosus (LE)[**22**].

Rerknimitr et al. evaluated the efficacy and safety of pulsed-dye laser (PDL) for DLE in a double blinded, randomized, controlled fashion. Forty-eight DLE lesions from nine patients were recruited. The lesions on one side of the body were randomized into the treatment group and the other side served as a control. Treatments with the PDL (595 nm) were delivered every four weeks for four consecutive months. The patients were evaluated at weeks 0, 4, 8, 12, 16 and 24. Erythema index (EI) and Texture index (TI) were obtained by Antera3D®. Modified Cutaneous Lupus Erythematosus Disease Area and Severity Index (mCLASI) and physician global assessment (PGA) scores were assessed in every visit. Lesional skin biopsies before and after the PDL treatment were taken from four patients. The lesions treated with the PDL demonstrated significantly more decreases in EI, TI and improvement in PGA scores compared to the control. Though there was improvement of mCLASI in the laser group, the significance difference was not observed. Interestingly, real-time polymerase chain reaction showed a reduction in CXCL-9, 10, IFN-γ, IL-1β, TNF-α and TGF-β. Additionally, post-treatment DLE lesions demonstrated decreased CD3, CD4, CD8 and CXCR3-positive cells. They concluded that improvements of DLE could be achieved with PDL [**9**].

Erceg et al. conducted an open prospective study to assess the efficacy and safety of PDL for the treatment of recalcitrant CDLE, using a validated scoring method and a fixed treatment schedule. Twelve patients with active CDLE lesions were treated with PDL (585 nm, fluence 5.5 J/cm2, spot size 7 mm) 3 times with an interval of 6 weeks followed by a 6-week follow-up period. Treatment outcomes were evaluated by 3 observers using the validated Cutaneous Lupus Erythematosus D isease Area and Severity Index (CLASI). Cosmetic results and adverse events were recorded. A significant decline in "active" CLASI was observed after 6 weeks, after 12 weeks, and at followup. Baseline active CLASI was 4.4 6 0.2 (mean 6 SEM), reaching 1.3 6 0.3 after follow-up (P \.0001). Individual scores for erythema and scaling/hypertrophy significantly declined 6 weeks after treatment. The "damage" CLASI (dyspigmentation, scarring, and atrophy) did not show any significant change during or after therapy. The observed clinical improvement was confirmed by two independent observers by clinical assessment of photographs (r = 0.87 and r = 0.89; both P \.05). The treatment was well tolerated, only minimal pain was reported, and the cosmetic result was fair. They concluded that PDL treatment was an effective and safe therapy for patients with refractory CDLE. PDL treatment may be considered for the treatment of stable, solitary, active CDLE lesions, when topical and/or systemic therapies have failed or are contraindicated [**2**].

Zoccali et al. reported a case of oral lupus erythematosus successfully treated with CO2 laser12. *Emer* et al. indicated an improvement in lupus pernio with the successive use of pulsed dye laser and nonablative fractional resurfacing. Pulsed dye lasers have been used in adults to treat refractory cutaneous lupus erythematosus (CLE)13. *Yelamos* et al. reported a case of pediatric cutaneous lupus erythematosus treated with pulsed dye laser [**64**].

Tumidus subtype (LT) has been recently separated from the chronic subtypes and is now considered an independent entity due to its particular clinical and histological features. Different treatments are usually prescribed for CLE. *Truchuelo* et al. have experience of CLE effectively treated with pulsed dye laser (PDL). They performed on 10 patients with histologically confirmed LT treated with PDL. All patients were treated with 595 nm PDL using the 10 mm spot size at 0.5 ms pulse width and a fluence of 8 J/cm2. Biopsies were taken before and 4 weeks after treatment and were stained with haematoxylin-eosin. Evaluation after PDL treatment showed clinical improvement in all of them without side-effects and reduction of the dermal lymphocytic infiltrate in 9/10 of the patients. Epidermal changes were absent in all patients. Mucin deposition persisted only in one patient. However, 50% of the patients developed new lesions nearby or distant to the treated zones. They concluded that PDL therapy was an effective and fast treatment option for acute fl ares of LT; however, it didn' t not prevent recurrences. A histological improvement had been confirmed in this study. Purpura seems to be necessary to achieve a good response. *Diez* et al. decided to study the histological changes induced by PDL. A prospective study was performed on nine patients with histologically confirmed CLE treated with PDL. Biopsies were taken before, immediately after, and 4 weeks after treatment and stained with hematoxylin and eosin and with commercially available antibodies to intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1. Evaluation after PDL treatment showed a significant reduction of the dermal lymphocytic infiltrate in six of nine patients (66.7%) and an important reduction of the basal damage in six of seven patients (85.7%). Other epidermal changes improved in four of six patients (66.7%). Mucin deposition persisted in two patients. ICAM and VCAM expression was reduced in seven of seven patients (100%) and five of six patients (83.3%) (p<.05). Clinical improvement was present in eight of nine patients (88.9%), without side effects. They concluded that PDL therapy could be an effective treatment for CLE. Immunohistologic improvement has been confirmed in this study [**16**].

Park et al. also reported a case of treatment of refractory discoid lupus erythematosus using 1,064-nm long-pulse neodymium-doped yttrium aluminum garnet laser [**17**].

Tremblay and Carey reported a case of atrophic facial scars secondary to discoid lupus erythematous: treatment using the Erbium: YAG laser [**24**].

Levy reported a case of intense pulsed light treatment for chronic facial erythema of systemic lupus erythematosus. Improvement was noted after the first session and 75% clearance was observed at 1 month after a second session. There were no adverse effects associated with the treatment. One year later it was observed that the results of the two treatments had been maintained [**45**].

Walker and Harland reported a case of carbon dioxide laser resurfacing of facial scarring secondary to chronic discoid lupus erythematosus [**47**].

Kuhn et al. reported a case of successful treatment of discoid lupus erythematosus with argon laser. After 2 laser applications, a significant improvement was observed and after 5 sessions of argon laser therapy the treated skin lesions had completely resolved with an excellent cosmetic result. The patient tolerated the laser treatment well without any short-term side effects. These data indicate that argon lasertherapy might be a powerful alternative approach in the treatment of vascular skin lesions of DLE [**48**].

Two patients with juvenile dermatomyositis, 5 with chronic discoid lupus erythematosus were treated for their teleangiectasias of the face with argon laser. The results were highly satisfactory with an almost normal appearance of treated skin in 4 patients. Two patients showed satisfactory results with 60-70% blanching, while 2 patients showed some improvement, but not a completely cosmetically satisfactory result. The most impressive results were in the patients with juvenile d ermatomyositis and Rothmund-Thomson's Syndrome. The only side effects observed were a slight scarring and an insignificant pigmentation. No patient displayed any signs of disease activation [**53**].

Refractory DLE patients treated with different lasers and intense pulsed light (IPL). Sixteen patients with histologically confirmed DLE participated in one study. Many patients had marked scarring. Pulsed dye laser (PDL) and IPL were used with low fluencies. Of 16 pat ients, 14 were improved regarding itching, erythema, scaling, scarring and pain. There was no scarring as a side effect of laser therapy or IPL. Two patients were not satisfied: one because of long healing time, and the other because of post inflammatory hyper pigmentation. IPL and PDL is a safe adjunctive therapy to conventional treatment of DLE. In the effort to prevent severe scarring and disfigurement it should be used as early as po ssible. Quality of life in patients with cutaneous lupus is severely impaired and one factor related to poor quality of life is the severity of the disease. Lasers have been described as successful in different expressions of CLE, mostly in cases of DLE. Gupta and Roberts described excellent results using pulsed dye laser (PDL) in a woman with SCLE. Henderson described a successful result in a patient treated with a CO 2 laser already in 1986 and Zachariae reported good results with an argon laser on teleangiectasias in different connective tissue diseases including DLE, but there were side effects such as scarring and hypopigmentation. Classical drugs in LE, such as choloroquine and thalidomide, have been shown to reduce skin lesions in LE partially through inhibition of angiogenesis. Therefore selective photothermolysis of oxyhaemoglobin with PDL (585 nm) was one of the first lasers described as effective for DLE. The Yttrium Aluminium Garnet (YAG) 1064 nm laser has also demonstrated improvement after three treatments with a three-week interval. *Diez* et al. have, in a prospective study, conducted histological and immunohistological examinations, before, immediately after and four weeks after PDL. The histology results were correlated with the similar excellent clinical results. A significant reduction of the dermal lymphocytic infiltrate and an important reduction of the basal damage were seen. PDL and/or IPL treatment are efficient and safe for early lesions of CLE as well as therapy resistant DLE. Although a lot already has been written regarding laser treatment of DLE, it is still quite controversial. Therefore, the majority of patients were considered therapy resistant and had gone through many other treatments before they were admitted to laser treatment. One possibility could be that traditional therapy for DLE does not include laser treatment as it has been a belief that laser therapy might deteriorate DLE. Another reason for not admitting patients to laser therapy could be that there are not so many hospitals that can offer PDL or IPL. The hopeless feeling that nothing helps can sometimes overwhelm the patients, thus leading to neglect concerning having their disease. It is

quiet common that both the patient and the treating physician lack knowledge regarding the laser or IPL as an adjuctive treatment of DLE. Patients' neglect concerning having their disease was also quite frequent. There is a long tradition of treating with medications. However, a Cochrane review from 2009 concludes that there is currently insufficient evidence to guide clinicians in the treatment of severe DLE. One could argue that the patient ' s non-compliance with both medication and the sun had contributed to bad treatment results. Especially the recommendation of sun avoidance given by us doctors mostly was not followed by the patients. However, it is important to listen to the patient properly, to discuss the treatment options and side effects in order to improve the patients ' trust and compliance. Patients could stop the treatment with antimalarials because of side effects (such as nausea and accommodation problems), lack of information or because of ineffective results. The scarred face and forced sun-avoidance could cause a feeling of alienation. The " wolf- like" appearance is a result of frequent scarring, if the treatment is not successful or the patient is not compliant, and is stigmatizing. The pilosebaceous unit appears to be one of the targets of the inflammatory process in DLE leading to a permanent destruction of the pilosebaceous follicle. The damage to the follicular stem cells may explain the irreversible alopecia and the scarring process which characterize the disease. There have been some discussions as to whether the laser treatment in itself could cause scarring. Scarring can occur with the lasers or IPL when treating carelessly with too high fluences, but the disease in itself often causes scarring. One of the suggested mechanisms for the therapeutic effects of PDL in LE is the growing evidence that endothelial cells play a major role in the inflammation and systemic manifestations of LE. The selective mechanism is selective destruction of the cutaneous microvasculature, which might modulate the inflammatory network, leading to regression of DLE. The dermal vessels may play an important role in the pathogenesis of lupus plaque, facilitating the access of activated T Lymphocytes to the lesion. We do not know the exact role that endothelial cell adhesion molecules (ECAMs) play in this and other inflammatory cutaneous disorders; however, we do have positive experiences with laser and IPL treatment in other autoimmune diseases for instance scleroderma regarding improvement in microstomia and in cutaneous sarcoidosis. Therefore expert recommendations are: 1) Treat the patients as early as possible with PDL laser or IPL to try to avoid the scarring, as not even a heavy covering foundation make-up could cover the scarring. 2) In case of persistent scarring one should consider vaporization with a CO2 laser or an erbium laser. The skin will not be restored to normal but will be much easier to cover with foundation.3) In case of insecurity of the diagnosis a biopsy should be taken as DLE can mimic other diseases. It also points out that maintenance therapy can be useful in severe cases. IPL and PDL could be safe and effective in DLE. We therefore can suggest early PDL or IPL treatments as an adjunctive therapy to conventional therapy for DLE with the purpose of trying to decrease the symptoms and to prevent scarring and disfiguring of the patient [**53,60**].

Becker et al. reported the successful treatment of a patient with hyperpigmentation caused by long-term antimalarial therapy for cutaneous lupus erythematosus. Clinical lightening of the darkly pigmented lesions was seen after a single treatment, and a significant improvement was observed after 3 laser applications. The patient tolerated the laser therapy well without any short-term side effects and did not experience either scarring or considerable textural skin changes. Histologic examination was performed before and after laser treatment to confirm the reduction of the pigment deposits. They concluded that trea tment of nonmelanotic skin hyperpigmentation with the Q-switched ruby laser could be a safe and powerful therapeutic method [**49**].

Although many CTD have been treated with pulsed dye laser, evidence-based recommendations are lacking. Varying levels of evidence exist to support the efficacy of the PDL in the treatment of different CTD. PDL treatment was given for chronic discoid lupus erythematodes (CDLE) lesions (27 patients), for tela ngiectasia and erythematous patches in patients with systemic lupus erythematodes (SLE) for subacute cutaneous lupus erythematodes (SCLE) lesions (3 patients), and for lupus tumidus (LT) (2 patients). Outcome measures included estimated clearance rate

and modified Cutaneous Lupus Erythematosus Disease Area and Severity Index. In chronic discoid lupus erythematodes: *Raulin* et al. (LOE 4) described PDL treatment of 8 patients with CDLE in a retrospective study and showed a clearance rate of 57.5% after an average of 4 treatments (ranging from 1-6). One study described a significant improvement of CDLE lesions after PDL treatment. A recently published study confirmed these findings. Conclusion is Grade C for CDLE (3 publications with LOE 4). PDL seems an effective therapeutic option for localized CDLE. In systemic lupus erythematodes, *Nunez* et al. (LOE 4) described for the first time the treatment of 4 patients with SLE using PDL and showed a clearance rate of 75%. Similar results were founded by *Baniandres* et al. (LOE 4) describing an average clearance of 68.0% (range 50%-80%) after 4.2 (range 1-10) treatments in 5 patients. Another case series (LOE 4) confirmed these findings. One case report (LOE 5) described complete clearance after 3 PDL treatments. Conclusion is Grade C for SLE (3 publications with LOE 4). PDL seems an effective therapeutic option for SLE. In SCLE and LT, 3 patients with SCLE (LOE 5) showed marked improvement after PDL treatment and 2 patients with LT (LOE 5) showed a significant reduction of erythema and scaling after PDL treatment. Conclusion is Grade D for the treatment of SCLE (3 patients) and LT (2 patients). PDL in SCLE and LT seems effective in a small number of patients. Evidence of laser treatments for SLE, CDLE, SCLE is of a low level, such as grade C and D. Although the incidence of these skin diseases, is quite low, it is unlikely that large randomized trials will be performed in the near future to position the PDL for these skin diseases. Most of these lesions are located in the facial area/chest and can be recalcitrant to conventional therapies, thereby giving a lot of emotional distress. Therefore, despite the low level of recommendation, treatment with PDL is still worth consideration, especially when topical and/or systemic therapies have failed or are contraindicated. Because of the light sensitivity of some of these diseases, one should be extra cautious when treating these lesions with PDL. Because of its vascular selectivity, the flashlamp-pumped pulsed dye laser (585 nm) is efficacious in the treatment of vascular lesions and is successfully used for the treatment of port-wine stains and haemangiomas in children. Based on the encouraging results with these cutaneous vascular disorders, the cutaneous lesions of patients with lupus erythematosus (LE) have now also been treated with the pulsed dye laser. Cutaneous lesions in lupus erythematosus are often difficult to treat with readily available local therapeutic methods. *Raulin* et al. reported here on a group of 12 patients whose LE lesions were treated with the pulsed dye laser. In 10 patients, the LE was limited to the skin, while two patients had systemic LE (SLE). Even in the two patients with SLE, a significant improvement of skin lesions was achieved. After a mean number of 51 laser sessions, a median clearance rate of 70% was attained for nine patients. In one case, the laser treatment failed to clear the lesions. Two patients did not show any visible improvement of the lesions, but pain and itching were significantly reduced. There were few side-effects. No prolonged laser-induced scarring occurred and in only two patients was hyperpigmentation seen, which had resolved completely after 4 and 5 months, respectively. During a median follow-up of 7 months (range: 3-32 months), only one patient (after a complete clearance of the skin lesions) had a small relapse. The pulsed dye laser could be an effective therapy for the treatment of superficial skin lesions in LE. In dermatology, the pulsed dye laser (PDL) is the therapeutic instrument of choice for treating most superficial cutaneous vascular lesions. In addition, clinical experience over the last decade allowed us to treat patients with an ever increasing number of non-vascular indications. For viral skin lesions, PDL proved to be an alternative to other therapy options. This applies particularly to periungual warts and mollusca contagiosa. The mechanism of PDL with inflammatory dermatoses has not yet been elucidated. The effect seems to be better if there is a vascular component to the disease. With most of these indications (such as psoriasis and acne), PDL currently plays a rather minor or complementary role. Regarding collagen remodelling (hypertrophic scars, keloids, stretch marks, and skin rejuvenation),the question of whether a therapy makes sense or not has to be decided from case to case. With PDL, it is possible to achieve goo d results with numerous, partly less well-known indications like lupus erythematosus. With other diseases, PDL has so far been considered to be a complementary therapy me

thod or to be in an experimental state. Long-term studies in large groups of patients are clearly needed[**53**].

Sriram studied autologous platelet rich plasma in the management of non-healing vasculitic ulcers of CTD. Out of the 20 patients, seven had systemic lupus erythematosus (SLE), three had rheumatoid arthritis (RA), two had dermatomyositis, three had Sjögren's syndrome, two had mixed connective tissue disorder (MCTD) and three h ad unclassified vasculitis. Patients with biopsy-proven vasculitic ulcer with no tendency to heal even after 6 months of high-dose steroids and immunosuppressive therapy were included in the study. Patients who were n ot willing to undertake the procedure or follow-up, who had active infection, platelet abnormalities in peripheral smear, uncontroll ed diabetes mellitus, obesity, uncontrolled hypertension or who were active smokers, were excluded from the study. A complete blood count, coagulation profile, immunological profile, diabetic status, wound culture and sensitivity, human immunodeficiency virus testing and ulcer biopsy were done. Activated PRP was applied over the ulcer by spraying using a syringe. Weekly dressing was done until the ulcer healed and healing was monitored using the Leg Ulcer Measurement Tool (LUMT). On average, epithelization of the wound occurred at 4.4 weeks. Faster healing was seen in mixed connective tissue disease (average 3.5 weeks) and delayed healing in systemic lupus erythematosus (average 4.7 weeks). Average platelet count obtained int he PRP was 5.52 lakhs/mm3 to 18.6 lakhs/mm3 with an increase in platelet count of 3.4- to 6-fold, respectively. Duration of healing corresponded with the platelet concentration in the prepared PRP. All the 20 patients showed complete healing within 6 weeks. PRP could be a safe, effective, outpatient procedure for the treatment of chronic recalcitrant vasculitic ulcers of CTD which improves the quality of life of patients and reduces their financial burden. PRP is an emerging biotechnology which has raised hopes in stimulating and accelerating healing of complicated wounds. Numerous proteins are contained in the alpha-granules of platelets: platelet-der ived growth factor (PDGF), transforming growth factor (TGF), platelet factor interleuki n (IL), platelet-derived angiogenesis factor (PDAF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin-like growth factor (IGF) and fibronectin,7 factor V, factor 8 (von Willebrand factor), thromboxane A2 and calcium. Owing to thes e mediators, platelet aggregates are form ed, which causes platelet stabilization by cross-linked fibrin and sticky glycoproteins. The fibrin matrix thus formed, aids in the infiltration of tissues with monocytes, fibroblasts and other cells which play an important role in wound healing. The inclusion of leucocytes in PRP has a potential benefit to combat infection and regulate immune function. Platelets, upon activation, release their growth factors. Maximum (70%) growth factor release occurs in the first 10 min. Near complete release of growth factors occurs in the first hour. Hence platelets should be activated immediately before PRP application. However, platelets synthesize and secrete additional growth factors in their 7-day viable period. Hence, patients were advised a weekly follow up. The rate of wound healing is dependent on the number of platelets in the blood clot. Many advantages make autologous PRP an attractive therapeutic option, which include no risk of disease transmission, growth factors and cytokines introduction directly into the wound, restoration of metabolic processes, neovascularization and activation of local immunity. Application of PRP is a simple, safe and cost-effective in-office procedure for treating chronic non-healing vasculitic ulcers which requires only a minimal set-up and a reasonable expertise [**65**].

There is a paucity of clinical information on the treatment of port wine stains (PWS) with pulse dye lasers (PDL) in patients with connective tissue diseases. Systemic lupus (SLE) is characterized by increased skin fragility and the potential for pigmentary alterations. Additionally, medications used to treat SLE may alter patient responses to laser therapy. *Izikson* et al. described two complications, tense blisters and hypopigmentation, after PDL treatment of PWS in SLE. The apparent skin fragility in the patient who developed blisters is likely due to her underlying connective tissue disease. The blistering resolved over 5 weeks with superficial desquamation and no scarring. The skin basement membrane zone (BMZ) is an ultrastructurally defined area situated between the outer layer of

skin, the epidermis, and the inner layer of skin, the dermis. Bullous lupus, one of the manifestations of systemic lupus, occurs as a result of pathogenic autoantibodies against type VII collagen, located in the sub-lamina densa; these autoantibodies produce subepidermal blisters. Additionally, recent work has shown that autoantibodies against other domains of collagen VII also colocalize to the site of lupus band in non-lesional SLE skin. This suggests that even non-lesional skin in SLE may be primed for blistering responses from trauma or trauma-induced inflammation. This situation may be analogous to another traumainduced blistering disorder marked by anti-collagen VII autoantibodies, epidermolysis bullosa acquisita. Accordingly, patients with SLE may have increased skin fragility that can manifest clinically as subepidermal blisters after the trauma of laser therapy or the resultant inflammation. It is possible that the differences in side effects between these patients may have been due to the administration of methotrexate in the first patient, as its anti-inflammatory activity likely limited the extent of combined insult to the epidermal and dermal structures after PDL. Additionally, differences could be due to varied PWS locations in each patient and extent of sun exposure while on hydroxychloroquine. Importantly, there was no lupus flare in either patient after PDL treatment. Treatment of SLE patients with light sources should be approached judiciously. It is well-known that UVB and UVA 290–400-nm light exacerbates and provokes SLE and other connective tissue diseases. However, all three types of lupus with cutaneous manifestations may actually improve after PDL 595 nm. *Izikson* et al. reported that PDL treatment of PWS in SLE patients on hydroxychloroquine is generally safe, but may be associated with increased potential for skin fragility and hypopigmentation. Accordingly, physicians should counsel patients about these possibilities and treat such patients conservatively [**19**]. *Viney* et al. reported a case of cutaneous lupus erythematosus following argon laser treatment. It is known that ultraviolet light and non-ultraviolet frequencies (x-rays, visible light) can induce lupus manifestations. Two cases of discoid lupus erythematosus after argon laser have been reported. Argon laser, a visible blue or green beam, could provoke cutaneous lupus erythematosus even if there was no heat-induced burn. It is important to be aware of this adverse effect due to the widespread use of lasers in dermatology, particularly for the treatment of cutaneous lupus lesions. Vascular lasers for facial erythro-blotches could be contraindicated in patients with active systemic lupus erythematosus46. Haber and Stéphan reported a case of systemic lupus erythematosus following polyalkylimide dermal filler[**55**].

Dermatomyositis

Dermatomyositis is an inflammatory myopathy characterized by muscular weakness and specific skin findings. There are several forms of dermatomyositis, including adult idiopathic, juvenile, and amyopathic, and it may be associated with malignancy or with another connective tissue disorder. Dia gnostic criteria include proximal symmetric muscle weakness, high muscle enzymes, electromyographic or muscle biopsy evidence of myopathy, and a cutaneous eruption typically associated with the disease. Patients may have associated myositis-specific antibodies, such as anti-JO 1 (histidyl-tRNA synthetase), which occur in approximately 20–35% of affected individuals. Classic skin lesions include a symmetric violaceous macular ery thema progressing to poikiloderma and induration. Gottron's papules are violaceous papules distributed over joints, and Gottron's sign includes erythematous macules over the same areas. Common lesions also include periungual telangiectasias, a heliotrope periorbital violaceous eruption, and eruptions over the shoulders (the shawl sign) or over the lateral hips (the holster sign). Patients with dermatomyositis may develop hyperkeratotic plaques on the hands with fissures and scale (mechanic's hands). Patients with juvenile dermatomyositis have a high incidence of calcinosis cutis. Five patients with a diagnosis of dermatomyositis in three separate reports were shown to have significant improvement in telangiectasias, poikiloderma, or Gottron's papules after treatment with PDL or argon laser [**21**].

CREST syndrome

Calcinosis cutis is a chronic condition involving insoluble calcified deposits of the skin and subcutaneous tissue. It is commonly associated with autoimmune connective tissue diseases and can be a source of pain and fun

ctional disability. The likelihood of developing calcinosis varies among the autoimmune connective tissue diseases, with systemic sclerosis and dermatomyositis being the most commonly associated. Identification of therapy for this challenging disorder has been hampered by a paucity of large controlled trials. Although there is no uniformly effective treatment for calcinosis cutis, several surgical and medical therapies have demonstrated varying degrees of benefit in the treatment of calcinosis, including surgical excision, laser therapy, extracorporeal shock wave lithotripsy, diltiazem, minocycline, colchicine, and topical sodium thiosulfate, along with others. Recommendations for the diagnosis and therapy of calcinosis cutis in patients with autoimmune connective tissue diseases are discussed. Diseases associated with dystrophic calcinosis include systemic sclerosis, dermatomyositis, SLE, panniculitis, cutaneous neoplasms, and genetic defects of extracellular matrix proteins. The CO2 laser has been used to "vaporize" superficial calcinosis. In a case report by Chamberlain and coworkers, a patient with CREST was subjected to CO2 laser treatment; 6 affected digits received each a single treatment. The authors reported significant clinical improvement; wound healing required approximately 6 weeks. In a small case series, CO2 laser has been found to be effective in treating CREST-related calcinosis. The authors applied this treatment to 21 areas of symptomatic digital calcification in 6 patients with CREST. Complete resolution was seen in 12 areas, moderate response in 5, minor response in 2, and recurrence of calcinosis in another 2. Procedure-related infections were seen in 2 patients, which resolved completely with antibiotic treatment. Large calcium deposits may be the source of considerable morbidity secondary to tumor tenderness and functional disability. For palliation, complete surgical excision of larger lesions may be the treatment of choice, although calcification may recur locally on a smaller scale. Smaller superficial lesions, on the other hand, can be effectively treated with CO2 laser. The CO2 laser, developed in the 1960s, provides both surgical precision and a bloodless field, offering a useful alternative to scalpel surgery in certain situations. As palliative treatment for cutaneous calcinosis, this modality, though tedious, was both effective and well tolerated. One study evaluated this treatment in 6 patients with limited SSc. A total of 21 areas of symptomatic digital calcification of the fingers was treated. Complete resolution of symptoms occurred in 12; moderate response with partial improvement was seen in 5; little improvement was observed in 2; and recurrence of calcinosis was found in 2. Postoperative infections complicated the course in 2 patients, with complete resolution with the use of topical and oral antibiotics. Chamberlain and coworkers utilized CO2 laser vaporization to treat digital CREST-related calcinosis in a single patient over a 5-year period with significant improvement in symptoms. The treated digits took an average of 6 weeks to heal. The ulcers did not recur on the treated digits for more than 3 years [**66, 67, 68, 69, 70, 71**]. Lasers are precision surgical tools with the benefit of a bloodless field, and they have been used with success in the treatment of superficial calcinosis cutis lesions. In a patient with limited cutaneous scleroderma, carbon dioxide laser–treated hand lesions were well controlled and had not recurred within 3 years of treatment. In another study, 6 patients with systemic sclerosis with limited cutaneous scleroderma were evaluated for digital calcinosis cutis, with subsequent carbon dioxide laser treatment of 21 sites. Of the 21 sites treated, 17 had a response to therapy, with 12 sites showing complete resolution. Postprocedural infection was noted as a complication in 2 of the patients. In another patient, erbium-doped yttrium aluminum garnet laser treatment was used to successfully treat multiple superficial calcinosis lesions of the buttocks. These studies d emonstrate the potential utility of laser procedures for the treatment of superficial localized calcinosis cutis. Calcinosis cutis is a source of considerable morbidity and functional impairment in patients with ACTDs. Calcinosis is most commonly associated with systemic sclerosis and dermatomyositis, although it has also been reported to occur in the setting of all ACTDs. This disorder is challenging to treat, with no gold standard therapy available, although numerous therapies have demonstrated varying success in certain groups of patients. Procedural therapies, including surgical excision, laser therapy, and ESWL, can provide benefit for lesions amenable to removal. Medical therapies that have shown benefit in larger series of patients include diltiazem, minocycline, and colchicine. Topical sodium thiosulfate is a newer treatment that appears promising in initial stu-

dies. Large comparative or controlled trials evaluating calcinosis therapies are needed [**66**].

Telangiectasia are cardinal features of systemic sclerosis (SS) and calcinosis, Raynaud's syndrome, esophageal motility, sclerodactyly, telangiectasias (CREST) syndrome. The etiology of telangiectasia in these syndromes is unknown, but vascular dysfunction has been proposed. The telangiectasia of CREST have anecdotally been considered relatively resistant to pulse dye laser (PDL), the treatment of choice for classic telangiectasia. One study was designed to test whether SS/CREST telangiectasia require more treatments than sporadic telangiectasia and to identify clinical and histological features that could explain such an effect. Nineteen skin biopsies from patients with SS or CRESTand 10 control biopsies were examined and compared for features that may predict a differential response to PDL. Sixteen cases of SS or CREST treated with PDL between 1997 and 2007 were evaluated and response to treatment was comp ared with 20 patients with sporadic telangiectasis. Relative to normal skin, CREST/scleroderma telangiectasia exhibited thickened vessels in 17 out of 19 sections and thickened collagen fibers in the reticular or deep dermis in all sections. The number of treatments required to clear SS/CREST telangiectasia was approximately twofold higher. SS/CREST telangiectasia are more resistant to PDL but can be effectively cleared with more treatments. Telangiectasia are common in systemic sclerosis (scleroderma), where they are most commonly observed on the face and hands. Their occurrence is correlated with the presence of the anticentromere antibody. The etiology of telangiectasia in CREST syndrome is not known, but vascular dysfunction has been cited as a potential trigger, arising from various insults. Immune complex-induced and inflammatory responses lead to endothelial cell dysfunction, intimal proliferation, thrombosis, and vasospasm, resulting in vascular compromise. Other theories invoke a model in which vascular endothelial cell abnormalities incite mononuclear infiltration, with resulting perturbations in TH1 or TH2 activity and subsequently abnormal fibroblast activity and increased collagen deposition. In other studies, increased pericyte density was observed in microvasculature at the periphery of lesions. Pericytes, smooth muscle-like cells in the vessel walls of capillaries and venules, synthesize both matrix components and cytokines that activate fibroblasts. PDL treatment is extremely effective in the treatment of telangiectasia, based on selective photothermolysis of vascular targets. Anecdotally, the telangiectasia of CREST/scleroderma have been considered relatively resistant, but limited studies are available on the efficacy of PDL in scleroderma variants. No studies have assessed the utility of pulsed dye laser in CREST. *Halachmi* et al. set out to compare the telangiectasia of CREST to sporadic telangiectasia with respect to clinical appearance, histological features, and response to PDL. Prominent and numerous telangiectasia are a characteristic clinical feature of scleroderma. They examined the histological appearance of telangiectasia to identify differences between CREST telangiectasia and sporadic telangiectasia, in order to understand the relative resistance of CREST patients to pulsed dye laser, the gold standard for the treatment of telangiectasis and superficial blood vessels. The telangiectatic endothelium appeared thickened in 17 out of 19 sections. Sub-intimal hyperplastic changes were apparent in the adjacent small arteries of three patients. Perivascular infiltrating inflammatory cells were usually minimal or absent. Thickened collagen fibers in the reticular or deep dermis were seen in all sections (19/19). Calcifications were not seen in any patient, and there were no other histological features of scleroderma. These histological findings are consistent with a prior study using three-dimensional reconstructions of macular telangiectasia in scler oderma, which demonstrated a horizontal plexus of intercommunicating dilated vessels. However, this group reported greater inflammatory infiltrates in the scleroderma telangiectasia, prompting the authors to speculate that perilesional or intralesional mononuclear cells might be a source of angiogenic factors involved in the formation of the telangiectasia. The etiology of telangiectasia in general, and in CREST specifically, remains unknown. Models have not explained the predilection for hands, face, and mucosa, nor their tendency to expand in diameter over time. Venous hypertension as a cause seems unlikely in view of their rarity in the feet, where high venous pressures occur. As mentioned above, inflammatory infiltrates and perivascular col-

lagenosis are not characteristic features in the CREST. While Raynaud's phenomenon and telangiectasia are both present in CREST, telangiectasia is not prominent in primary Raynaud's disease, suggesting that telangiectasia are not a consequence of recurrent vasospasm or vasoconstriction. Furthermore, telangiectasia are common on the face, which is not affected by Raynaud's phenomenon. The treatment of telangiectasia with pulsed dye laser is based on the principle of selective photothermolysis. Previous studies with comparable treatment parameters to those used herein found that telangiectasia respond well to pulsed dye laser, with the majority being cleared within one to two treatments. These findings support this with the mean number of treatments required to clear the telangiectasis being 1.92, with larger lesions requiring more treatments. The authors founded that all telangiectatic lesions responded to treatment, but that CREST telangiectasia required approximately twice as many treatments as control lesions (3.24 vs. 1.92) across all lesion sizes. In light of the histological findings, it is plausible that the thickened endothelium of CREST contribute to their relative resistance compared to normal vessels. The target of laser treatment in vascular lesions is the hemoglobin within red blood cells. When these are heated by absorption of laser light, they transmit this heat to the vessel walls, thereby achieving the clinically desired effect. Since the target is the hemoglobin and not the endothelial cells themselves, it is not anticipated that longer wavelength lasers would overcome the need for more treatments; rather, the lasers that are most hemoglobin-specific, such as pulsed dye laser, should be the most effective in targeting these vessels [**72**].

Contraindications in CTDs

Mesotherapy involves multiple intradermal or subcutaneous injections of a mixture of compounds (plant extracts, homeopathic agents, pharmaceuticals, vitamins, and other bioactive substances) in minute doses, using very fine gauge needles, to treat medical (mainly local) and cosmetic conditions. The contrai ndications to mesotherapy include a body mass index greater than 30, known hypersensitivity to any of the components, less than 18 years of age, pregnancy, lactation, patients on anticoagulants, cardiac drugs (like amiodarone, hydralazine, calcium channel blocker, beta blocker), disease conditions like insulin dependent diabetes, liver and kidney disorders, AIDS, seizure disorders, Behçet' dise ases, urticaria pigmentosa, granuloma annulare and CTDs. Several environmental factors have been implicated in triggering or modifying CTDs. Such factors include infections, drugs, chemicals, ultraviolet light exp osure, dietary manipulation, and hormones [**73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87**]. *Colon-Solo* et al. report a case of a 31-year-old woman who developed SLE after mesotherapy with acetyl-Lcarnitine (ALC) used for weight reduction. ALC is known to have immunomodulating properties and could be involved in inducing or aggravating autoimmune disorders [**87**]. The contraindications to thread lifting also includes CTDs [**88**].

Cosmetical Procedures and Medication in CTD (Table 1)

Patients with CTDs have an increased risk of infection when compared with the general population. In addition, some medications used in the treatment of rheumatic diseases are immunosuppressive, further increasing the risk of infection. These drugs may also have an impact on wound healing. There is little data addressing perioperative risk acquired via direct clinical trial. Methotrexate (MTX) has been the most rigorously studied drug in RA patients undergoing surgery. On the basis of several studies, including a prospective randomized trial, MTX appears to be safe in the perioperative period. Hydroxychloroquine and sulfasalazine have favorable toxicity profiles, but have not been studied in the perioperative period of cosmetical procedures. Conflicting results have been published in regard to leflunamide use in this setting. A si gnificant increase in wound healing complications has been reported in leflunamide-treated patients (40%) compared with MTX treated patients (13.6%). However, a contrasting study found no difference comparing 41 patients given continuous leflunamide when compared with 41 patients in whom the leflunamide was stopped 1 month prior to surgery. Pending definitive studies, the authors are recommended holding leflunamide and sulfasalazine until normal postoperative bowel and renal function has been demonstrated. Biologic agents such as the TNF inhibitors have been used in the treatment of RA now for over a decade. The major complica-

Table 1. Recommendations for the Management of CTDs With Cosmetical Procedures

1. **General principles**
- There is no universally effective cosmetical treatment for CTDs or an accepted therapeutic algorithm
- The score systems and serum levels of acute phase reactants (CRP/ESR) are used to measure CTDs activity.
- These procedures shoould be done inactive period of CTDs.
- This treatments can be considered an adjunctive therapy
- If the diagnosis is unclear, skin biopsy can help to confirm the presence of CTDs

2. **Procedural therapy**
- Fillers, botulinum toxins, autologous fat transplantations, PRP and lasers were succesfully used to correct the atrophic and scatricial defects during inactive period of CTD
- Fillers: It might be suitable in inactive period of CTDs like end-stage scleroderma. Calcium hydroxyapatite, methacrylate, acrylamides, silicone and polyalkylimide produced notable chronic activation of the immune system. Hyaluronic acid elicited little immune response. The plasma levels of myeloperoxidase and the chitin-like proteins chitotriosidase and YKL-40 may be important markers indicative of immune response activation in certain cases. Empiric treatment should begin with macrolide or tetracycline in these patients.
- Botulinum toxins: Cases of dyspareunia, headaches and thoracic outlet syndrome caused by localised scleroderma were treated with botulinum toxin injections.
- PRP, low level lasers, ultrasound have been used non-healing vasculitic ulcers of CTD and they can facilitate the healing of chronic digital ulcers and Raynaud's phenomenon.
- Calcinosis cutis: Laser (carbon dioxide or Er:YAG) can be considered for discrete superficial lesions. Extracorporeal shock wave lithotripsy may decrease lesion size and pain
- Autologous fat transplantation: Lupus profundus and scleroderma-induced facial atrophy have been successfully treated with fat transplantation.

3. **Lasers**
- Treat the patients as early as possible with PDL laser or IPL to try to avoid the scarring.
- In case of persistent scarring one should consider vaporization with a CO2 laser or an erbium laser.
- In case of insecurity of the diagnosis a biopsy should be taken as DLE can mimic other diseases.
- IPL and PDL could be safe and effective in DLE, scleroderma and dermatomyositis.
- Lasers can not prevent recurrences
- Purpura seems to be necessary to achieve a good response.
- Cessation of smoking is strongly recommended.

4. **Mesotherapy and thread lifting are contrindicated in CTDs.**

tion of therapy with TNF inhibitors is infection. Gram-positive organisms are the most commonly reported bacteria complicating TNF inhibitor therapy and are the predominant organisms seen in early surgical site infections. A single small prospective study by *Bibbo* et al. addressed surgical risk in patients undergoing foot and ankle procedures and found no increase in the 16 patients who were treated with continued perioperative TNF inhibitors, in contrast with the 15 patients treated with other DMARDS, who had delayed healing. In a retrospective study of RA patients undergoing orthopedic surgery, 10 of 91 patients developed a serious postoperative infection. Seven of those 10 patients were receiving TNF inhibitor therapy. Other factors such as age, steroid use, or diabetes were not significantly different between the groups. Some information can also be extrapolated from the experience using TNF inhibitor therapy in inflammatory bowel disease patients. When operative complications in 40 patients with Crohn's disease CD) treated with a TNF

inhibitor, infliximab, at the time of bowel resection were compared with 39 CD patients not receiving infliximab, no significant differences were seen. Until there are definitive studies addressing this question, given the known increase in infection with these agents, it seems prudent to discontinue TNF inhibitör therapy preoperatively. This position has also been advocated by European investigators. Rituxamab is a monoclonal antibody directed against the CD-20 cell surface marker, which is present on the surface of a subset of B- lymphocytes. Risk of infection with rituxamab is comparable with the risk seen with other biologic agents in clinical trials in RA, but there are no data regarding its use in the perioperative setting. Immunoglobulin levels are decreased, with a disproportionate decrease in autoantibody levels. Since the depletion of B cells can persist for up to a year, surgical planning to minimize risk is difficult. Many rheumatic disease patients receive chronic glucocorticoid therapy. Concern about adrenal suppression in patients chronically given exogenous glucocorticoids with reports of adrenal insufficiency during periods of stress has led to the use of supraphysiologic doses of cortisone, or "stress dose steroids." Glucocorticoid therapy is well recognized as a significant risk for infection and delayed wound healing. Patients have traditionally been given augmented doses if they have received low-dose steroid therapy for >6 months or moderate- to high-dose therapy for more than 3 weeks. However, the length of steroid therapy and dose are not reliable predictors of need in the perioperative period. Moreover, commonly used tests to assess adrenal function do not accurately predict steroid need. When 40 patients receiving chronic steroid therapy, 63% of whom had demonstrated adrenal insufficiency by the cosyntropin stimulation test, were hospitalized with significant stresses, none developed clinical adrenal insufficiency receiving only their usual daily dose of steroid. Additional support for this comes from a prospective study of patients on chronic steroid therapy randomized to receive their usual daily dose of steroid or stress doses at the time of surgery. Although all of these patients had demonstrated adrenal insufficiency by ACTH stimulation test, there was no difference clinically between the groups. The magnitude of the normal endogenous steroid response to various surgical procedures has been defined. Thirty patients who had never received exogenous steroid undergoing either arthroscopy or unilateral knee arthroplasty had serial cortisol levels measured. There was no significant increase over baseline cortisol levels in the arthroscopy patients, but there was a significant increase in endogenous steroid in the arthroplasty group. These studies support limiting the routine use of stress dose steroids in the perioperative setting. Patients undergoing minor procedures should take only their usual Daily steroid dose [**58**].

Summary

AThe use of lasers in the treatment of cutaneous manifestations of CTD may offer patients long-term benefit with reduction or complete clearance of skin lesions. The majority of the evidence in the dermatology literature for the use of lasers in the treatment of various cutaneous lesions of lupus, scleroderma and morphea, and dermatomyositis is largely limited to small case reports and series. Most of the disease entities reviewed demonstrated some benefit from treatment with lasers, although not without risk of adverse events, including scarring and dyspigmentation. The greatest number of reports are on laser treatment of cutaneous LE, with pulsed dye, argon, CO2, and erbium and neocymium-doped YAG lasers and IPL. Successful treatment of linear and plaque morphea; related telangiectasias, microstomia, sclerotic bands, digital calcification, and ulceration; and perioral rhytides have also been reported using various lasers. Telangiectasias, poikiloderma, erythema, and Gottron's papules associated with dermatomyositis have also been successfully treated using lasers without any report of adverse effects. Its main limitation, namely the small number of published studies, reflect the importance of this review of the dermatology literature on the use of laser devices in the treatment of CTD. Furthermore, a number of reports were published more than 20 years ago, discussing use of devices, parameters, and techniques that may not be routinely used with current laser treatment. Protocols using longer pulse durations and lower energies are likely to be associated with fewer adverse events. More-recent reports of lasers in the treatment of the four CTD reported herein offer relevant evidence that lasers may be used in CTD safely and with good benefit to patients with these conditions. The predominantly retrospective

nature and small sample size of the case reports and series limit this evidence. Better designed and larger studies are clearly needed in thetreatment of these medically important cutaneous lesions associated with CTD processes. Although a review of the evidence derived from predominantly case reports and series is promising, randomized controlled trials and reports of treatment using current laser devices, parameters, and techniques are needed to further evaluate and determine the proper placement of lasers in the treatment armamentarium of CTD. The wide range of dermal fillers available for use in facial esthetics makes it essential to have a thorough knowledge of the relevant product characteristics. Clinicians must have a sound understanding of facial anatomy and be suitably trained and experienced to ensure correct product selection, preparation, and injection technique. Appropriate patient selection is vital, and the importance of fully investigating the patient's previous medical injection history prior to treatment should not be underestimated. The majority of complications are related to sterility, placement, volume, and injection technique. Small, slow, deep injection with massage should be considered at every procedure to introduce the product gently and evenly. Clinicians should be fully aware of the signs and symptoms related to complications and be prepared with agents readily available in the office to enable them to act swiftly and proactively. Adverse events and the treatment options are not discrete. A broad knowledge and in-depth investigations are important for satisfactory management and outcome. Equally, collecting and sharing adverse reactions is important to improve our knowledge and to the development of consistent, effective protocols. Finally, clinicians should always consider seeking advice from a trusted colleague.

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