Published in final edited form as:
Curr Opin Rheumatol. 2010 January ; 22(1): 78–84. doi:10.1097/BOR.0b013e328333b9e2.

Rheumatic Manifestations of Skin Disease

Jennie T. Clarke[1] and **Victoria P. Werth**[2]

[1] Department of Dermatology, Hershey Medical Center

[2] Philadelphia V.A. Medical Center

[3] Department of Dermatology, University of Pennsylvania

Abstract

Purpose of review—There is increasing interest in improving the understanding of pathophysiology, outcome measures, and therapies of rheumatic skin disease. Increasingly studies are using the skin as a primary endpoint for evaluating therapies. This will review the current state of the art for the most common rheumatic skin diseases.

Recent findings—A number of medications, including biologics such as TNFa and interferon, have been associated with onset of cutaneous lupus. The cutaneous lupus erythematosus area and severity index (CLASI) has been further validated and utilized in a number of studies. Smoking continues to be associated both with presence and refractoriness of CLE to therapy. There are several tools now available for evaluating the skin disease of dermatomyositis, but there is a need for new effective therapies. Measurement of skin disease in scleroderma continues to be a challenge, and there is a need for more effective therapies. Several studies show efficacy of intravenous iloprost for severe Raynaud's and skin ulcers, and of bosentan for digital ulcers.

Summary—This review covers new outcome measures, treatments, and unusual manifestations of cutaneous lupus, dermatomyositis, scleroderma, and rheumatoid arthritis. There have been a number of new studies related to validation of disease activity measures, as well as their use in evaluation of new therapies for these conditions. Validated outcome measures are required to perform meaningful studies, and will facilitate organized epidemiologic, quality of life, and therapeutic studies.

Keywords

Cutaneous lupus erythematosus; Dermatomyositis; Scleroderma; Rheumatoid arthritis

Introduction

Recent advances in the understanding of cutaneous findings in cutaneous lupus erythematosus (CLE) and systemic LE (SLE), dermatomyositis, systemic sclerosis, and rheumatoid arthritis in terms of clinical evaluation, triggers of disease, outcome measures, systematic clinical studies, and treatment will be discussed.

Cutaneous LE includes lupus specific and lupus nonspecific skin lesions. Lupus specific skin lesions include chronic cutaneous LE, subacute cutaneous LE and acute cutaneous LE [1,2]. Chronic cutaneous LE includes localized, generalized, and hypertrophic LE, lupus panniculitis, lupus tumidus, and lupus pernio. The criteria for SLE include four dermatologic

Corresponding Author: Victoria P. Werth, M.D., Department of Dermatology, Hospital of the University of Pennsylvania, 3600 Spruce Street, 2 Rhoads Pavilion, Philadelphia, PA 19104-4283, Phone: (215) 823-4208, Fax: (866) 755-0625, werth@mail.med.upenn.edu.

criteria, some of which are potentially overlapping. Patients can meet four criteria for SLE based solely on dermatologic findings, and some of these patients are not systemically ill [3]. These criteria include malar rash, photosensitivity, discoid lesions, and oral ulcers. Patients with lupus nonspecific skin lesions are more frequently systemically ill with SLE relative to patients with lupus specific skin lesions [4]. Medications are a frequent trigger of SCLE, and the list of drugs that are associated continues to expand. There have not been many systematic studies of CLE [5]. With the development of the Cutaneous Lupus Area and Severity Index (CLASI), a validated outcome measures for cutaneous LE, it is hoped that more systematic epidemiologic and therapeutic trials will be performed [6,7].

Skin lesions in dermatomyositis are frequently clinically distinctive, with pathognomonic lesions including Gottron's papules with lesions targeting over joints, and characteristic lesions including a heliotrope, periungual telangiectasias, dystrophic cuticles, and photodistributred violaceous erythema. Biopsy of the skin for routine histology frequently looks identical in cutaneous lupus and dermatomyositis.

Cutaneous findings are manifestations important in the classification systemic sclerosis (SSc). Raynaud's phenomenon may precede the onset of SSc by years, especially in localized cutaneous SSc (lcSSc). Cutaneous sclerosis typically commences on the distal extremities. While gradual and often limited to these areas in lcSSc, in diffuse cutaneous SSc (dcSSc), the sclerosis is often preceded by nonpitting edema, rapidly progressive, and more diffuse. Telangiectases are prominent especially on the face. The skin is dry and often pruritic. Areas of hyper- and hypopigmentation may be seen. Painful digital ulcers arise as a consequence of ischemia.

Cutaneous manifestations of rheumatoid arthritis (RA) include rheumatoid nodules, rheumatoid vasculitis, granulomatous dermatoses. Patients with RA are at risk of developing psoriasiform cutaneous adverse reactions to TNFα inhibitors.

Cutaneous Lupus Erythematosus

Patients can have skin findings of CLE alone or have cutaneous LE associated with underlying systemic disease.

Cutaneous Findings in Cutaneous Lupus Erythematosus—There have been several recent reports about papulomucinous LE, otherwise termed lupus tumidus, as a subset of chronic cutaneous lupus. Patients with this variant tend to have negative ANA's, increased susceptibility to lesion induction with ultraviolet light, minimal changes at the dermal-epidermal junction on skin biopsy, and they frequently do not have other manifestations of SLE. Rarely these patients have concurrently other forms of cutaneous LE, thus suggesting that tumid LE fits, despite many differences from other forms of cutaneous LE, in the spectrum of chronic cutaneous LE. There is ongoing debate about the exact categorization of lupus tumidus [8].

Descriptions of the clinical appearance of cutaneous lupus, including those resembling acne and comedones in discoid lupus, emphasize the heterogeneous clinical presentations of cutaneous LE [9].

Two families have a well-defined mutation of TREX1. The mutant TREX1 enzyme diminishes TREX1 function and studies suggest a role for TREX1 in dsDNA degradation to prevent immune activation [10].

Oral lesions in lupus patients can be confusing. The clinical differential diagnosis of oral lupus lesions depends on whether the lesions are keratotic, ulcerated, lip lesions,

erythematosus purpuric macules, or bullous [11]. For instance, ulcerated discoid lesions have a differential that includes aphtha, erosive lichen planus, traumatic ulcers, deep fungal infection, Langerhans cells histiocytosis, and squamous cell carcinoma. Biopsy of oral ulcers due to lupus show pathologic changes identical to those seen in the skin, and typically do not indicate vasculitis.

Triggers—There are a number of triggers of cutaneous lupus. Several recent studies have examined the low but measurable output of UVB from compact fluorescent lights, suggesting that these should be covered in the setting of lupus patients [12,13]. Others have reported new medications or reviews of medications associated with subacute cutaneous lupus, including capecitabine and sertraline [14]. Anti-TNF medications continue to be reported in association with subacute cutaneous lupus, as well as injection-site reactions from interferon-beta that show lupus on biopsy.

Outcome measures—The absence of validated outcome measures for cutaneous lupus has hampered the ability to do clinical trials or perform careful clinical cohort studies. Recent studies have expanded the initial validation of the CLASI, examining the responsiveness of the CLASI in a trial, and extending validation to rheumatology [15,16]. Recognition of the need for core sets of data to systematically evaluate lupus populations have been developed [17].

Epidemiology/Organized studies—One study examined the incidence of cutaneous lupus over a forty-year period in Olmsted County, Minnesota and found an incidence rate of CLE of 4.3, with 19% progressing to SLE over a 20-year period [18]. The development of a web-based database for cutaneous lupus has allowed systematic characterization of the disease severity and quality of life of cutaneous lupus patients examined in an academic center. The most therapeutically resistant patients are more likely to be smokers, confirming this risk factor for refractory disease [19]. One study also confirmed that smoking is a risk factor for developing CLE [20]. A systematic study of anti-Ro/SSA-positive patients with skin manifestations demonstrated that these patients do develop new autoimmune diseases and are potentially at risk of drug-induced SCLE [21]. Pediatric DLE is rarer, but potentially more frequently associated with SLE, particularly when generalized [22].

Treatment of CLE—Sunscreens and sun avoidance are important aspects of treatment and prevention in CLE patients. As a result, patients frequently have low vitamin D levels and should be supplemented [23].

There have been extraordinarily few controlled trials for cutaneous lupus. Thus, most therapy is guided by case series, case reports, and expert opinion. Topical calcineurin inhibitors are used as adjunctive therapy [24]. Systemic therapy for disease that is scarring, unresponsive to topical therapy, or widespread involves hydroxychloroquine at a dose of <6.5 mg/kg/day. For therapeutically resistant patients, there is sometimes a benefit by adding quinacrine at a dose of 50–100 mg/day. Another study of LE tumidus demonstrated that 61% of patients had a complete or near-complete response to antimalarials, with smokers having higher initial clinical score and being less responsive to treatment [25]. A preliminary study of two refractory CLE patients suggested that one of the patients had some improvement with lenalidomide, although its use in SLE may be problematic because of risk of immune stimulation [26]. One open prospective study suggested that the pulsed dye laser can be effective in treating DLE [27].

Thalidomide is an effective therapy for refractory CLE. However, there is a high incidence of sensory axonal neuropathy, the total dose of thalidomide that can cause this is relatively

low, and recovery in one study occurred in 25% based on sural nerve sensory action potentials (SAP) [28].

Dermatomyositis

Dermatomyositis can involve only the skin (amyopathic) or have only mild muscle findings on lab testing without clinical symptoms or signs (hypomyopathic). Pathognomonic findings include Gottron's papules and Gottron's sign. Characteristic findings include a heliotrope, periungual telangiectasias, dystrophic cuticles, and photodistributed violaceous erythema.

Diagnosis—Skin biopsies should be obtained in patients where dermatomyositis (DM) is in the differential, largely to determine if the patient has an autoimmune skin disease. There is still confusion about how to diagnose amyopathic dermatomyositis, since these patients by definition do not have muscle disease and thus cannot fulfill the current criteria for dermatomyositis. Skin biopsy will not differentiate CLE from DM, and thus clinical-pathological correlation is key to making the diagnosis [29].

Triggers—There are a number of potential drug triggers of DM, including hydroxyurea, IFN-beta-1a, and TNF blockers [30–33].

Outcome measures—There have been few studies of dermatomyositis related to the skin. Hopefully, the development of validated tools will facilitate this process [34,35].

Systemic Sclerosis

Cutaneous changes are common, early manifestations of systemic sclerosis (SSc), important in the classification of this heterogenous disease. The two major subtypes, limited cutaneous SSC (lcSSc) and diffuse cutaneous SSc (dcSSc), are distinguished in part by the acuity and extent of cutaneous findings.

Cutaneous outcome measures—Skin sclerosis is one of the most common endpoints used in studying SSc; however, the relationship between sclerosis and disease morbidity and mortality is complex. A number of studies have linked the course and severity of cutaneous sclerosis with overall disease prognosis [36,37]. Rapid worsening of cutaneous sclerosis has been associated with renal crisis and reduced survival among patients with anti-topoisomerase antibodies [38]. More recently; however Shand, *et al*, applied a latent linear trajectory model to determine whether changes in modified Rodnan skin score (mRSS) are directly related to disease morbidity and mortality among dsSSc patients [39]. While, the highest mortality occurred among patients with the greatest baseline mRSS who had minimal improvement over time, those with high or low baseline mRSS who subsequently improved had as many or more systemic complications as those in the highest mortality group. An analysis of 1200 patients enrolled in the German Sytemic Sclerosis Network, revealed that patients with higher mRSS had a greater frequency of dysphagia, reflux, pulmonary fibrosis, digital ulcers, and joint contractures, but mRSS had no relationship with the frequency of any other systemic manifestation [40]. Complicating matters further is the tendency of cutaneous sclerosis to improve spontaneously over time in some patients and the use of disease modifying agents that may have altered the severity of skin findings by patients in these studies.

The measurement of sclerosis also poses challenges. While the fully validated mRSS has been considered the gold standard evaluative tool, its responsiveness has been somewhat modest in several trials, and it has been argued that it may not be sensitive enough to detect small but clinically relevant changes [41]. Additionally, the reliable administration of the mRSS requires training and experience [42]. Several other tools used include ultrasound

measurement of dermal thickness, durometer, elsatomer, twistometer, cutometer, and plicometer, but limitations to their use include lack of responsiveness in clinical trials, difficulty to administer or learn, poor reproducibility, or cost [43]. Recent recommendations from the Scleroderma Clinical Trial Consortium include the use of mRSS, durometry, and a visual analog scale in clinical trials of SSc [44].

Treatments—Therapies aimed at reducing cutaneous sclerosis are limited. Topical corticosteroids and calcineurin inhibitors are minimally beneficial as they fail to penetrate into affected dermal tissue. Phototherapy with wavelengths in the UVA spectrum has been shown to soften skin and reduce dermal thickness in sclerosing disorders including SSc [45–47]. Systemic immunosuppressive agents including corticosteroids, methotrexate, cyclophosphamide, and cyclosporine have been used with varing success to improve sclerosis. The role of D-penicillamine has been controversial, with benefits reported in open and retrospective trials [36,48] but with no difference demonstrated in a double-blind randomized controlled trial comparing high and low dosages [49]. A recent trial of mycophenolate mofetil combined with intravenous and oral corticosteroids demonstrated improvement in mRSS [50]. Conflicting results have been reported in two recent small trials of the anti-CD20 molecule, rituximab, with improvement in mRSS reported in one study [51], but not the other [52]. A lack of efficacy and an increased morbidity and/or mortality have been reported from trials of recombinant relaxin [53] and a recombinant anti-TGFβ1 antibody [54].

In addition to sclerosis, vascular pathology contributes to cutaneous manifestations of scleroderma including RP and digital ulceration. Treatment remains challenging. Intravenous iloprost is approved for the treatment of severe RP with ulcerations, and a recent open-label randomized trial demonstrated equal efficacy of low and high dose iloprost [55]. In Europe, the endothelin receptor antagonist, bosentan, has been approved for prevention of digital ulcers. To better predict those at risk for digital ulcers, Sebastiani *et al* ulitlized nailfold videocapillaroscopic data to create a mathematical model capable of predicting digital ulcers with a sensitivity of 85.9% and specificity of 94.3% [56].

Insights into the pathogenesis of SSc have led to potential novel therapeutics. Inhibition of histone deactylase-7 *in vitro* led to decreased type I and III collagen synthesis; this enzyme may be a potential therapeutic target in SSc [57]. The stimulatory effects of TGFβ on extracellular matrix synthesis are mediated by connective tissue growth factor (CTGF). Administration of an anti-CTGF antibody inhibited TGFβ-induced fibrosis in a murine model of fibrosis [58]. Finally, closer yet to bedside are tyrosine kinase inhibitors such as imatinib. By inhibiting platelet derived growth factor receptor signaling, they reduce cutaneous and systemic fibrosis as demonstrated by *in vitro*, animal, and human data [59,60]. Clinical trials of imatinib for SSc are ongoing.

Rheumatoid Arthritis

The pathomechanisms of the cutaneous manifestations of rheumatoid arthritis (RA) including rheumatoid nodules, granulomatous dermatoses, and rheumatoid vasculitis are unknown; however, immune complex deposition and/or small vessel vasculitis are likely important.

Rheumatoid Nodules—Rheumatoid nodules are the most common extra-articular manifestation of RA and occur in 20–30% of affected individuals. They are more common in males and in those with rheumatoid factor seropositivity. They appear as flesh-colored, firm, subcutaneous nodules that range in size from millimeters to several centimeters. They are usually painless and often occur over extensor surfaces or at sites of repetitive stress.

Nodules may shrink, persist, or worsen with RA treatment. Accelerated nodulosis, characterized by the abrupt onset or worsening of rheumatoid nodules, has been described following therapy with leflunomide [61], methotrexate, TNF-inhibitors, and with an aromatase inhibitor for breast cancer in a patient with RA [62].

Rheumatoid Vasculitis—The skin is involved in 75–89% of patients with rheumatoid vasculitis, often as the presenting sign of the condition [63]. Purpura, livedo reticularis, atrophie blanche, and ulcers are cutaneous signs of rheumatoid vasculitis. It is associated with longstanding, erosive, seropositive disease, and is more frequent in those with antibodies to citrullinated peptides [64]. TNF-inhibitor therapy has been associated both with onset and improvement of rheumatoid vasculitis [64,65]. Treatment with argatroban, an antithrombin agent, in a patient with antiphosphatidylserine-prothrombin complex antibodies led to resolution of ulcers refractory to immunosupresive therapy [66].

Granulomatous Dermatitis—Interstitial granulomatous dermatitis (IGD) and palisaded neutrophilic and granulomatous dermatitis (PNGD) are eruptions associated autoimmune diseases including RA. These eruptions represent reaction patterns related to cutaneous immune complex deposition [67]. The polymorphous eruption of IGD favors the trunk, thighs, and axillae in a symmetric fashion and is characterized by erythematous, indurated, linear bands, papules, nodules, or annular plaques. PNGD is characterized by symmetric papules and nodules on the extremities. Spontaneous resolution is common, but treatments including NSAIDS, prednisone, dapsone, colchicine, oral tacrolimus [68], and TNF-inhibitors [69] have been reported. TNF-inhibitors have also been linked to onset of the eruption [70,71].

Psoriasiform Eruptions Related to TNFα Inhibitor Therapies—Patients treated with TNFα inhibitors may develop an eruption that is clinically and histologically indistinguishable from psoriasis. This can occur in those receiving these agents for any condition; although those with RA appear to be at greatest risk. The eruption typically clears with drug cessation, and may or may not recur during treatment with other drugs of this class [72–74].

Conclusion

Skin manifestations are often prominent or at times sole features of lupus erythematosus, dermatomyositis, systemic sclerosis, and rheumatoid arthritis. The easy observability and accessibility of the skin for study has and will continue to enhance our understanding of the pathogenesis of these systemic diseases. The development of validated outcome measures is imperative for reliably objectifying the cutaneous manifestations of these diseases and their response to therapeutic interventions. Patient databases and multidisciplinary collaboration will enable the performance of larger and more meaningful clinical trials.

Acknowledgments

This study was supported by NIH K24-AR 02207 and a V.A. Merit Review Grant

Bibliography

1. Gilliam JN, Sontheimer RD. Distinctive cutaneous subsets in the spectrum of lupus erythematosus. J Am Acad Dermatol. 1981; 4:471. [PubMed: 7229150]
2. Werth VP. Clinical Manifestations of Cutaneous Lupus Erythematosus. J Autoimmun. 2005; 4:296.

3. Albrecht JA, Braverman IM, Callen JP, Connolly MK, Costner M, Fivenson D, Franks A, Jorizzo J, Lee LA, McCauliffe D, Sontheimer RD, Werth VP. Dermatology position paper on the revision of the 1982 ACR criteria for SLE. Lupus. 2004; 13:839. [PubMed: 15580979]

4. Yell JA, Mbuagbaw J, Burge SM. Cutaneous manifestations of systemic lupus erythematosus. Br J Dermatol. 1996; 135:355. [PubMed: 8949425]

5. Jessop S, Whitelaw D, Jordaan F. Drugs for discoid lupus erythematosus. Cochrane Database Syst Rev. 2001:CD002954. [PubMed: 11279785]

6. Albrecht J, Taylor L, Berlin JA, Dulay S, Ang G, Fakhazardeh S, Kantor J, Kim E, Militello G, McGinnis K, Richardson S, Treat J, Vittorio C, Voorhees AV, Werth VP. The CLASI (Cutaneous LE Disease Area and Severity Index): an outcome instrument for cutaneous lupus erythematosus. J Invest Dermatol. 2005; 125:889–894. [PubMed: 16297185]

7. Kreuter A, Tomi NS, Weiner SM, Huger M, Altmeyer P, Gambichler T. Mycophenolate sodium for subacute cutaneous lupus erythematosus resistant to standard therapy. Br J Dermatol. 2007; 156:1321–1327. [PubMed: 17408395]

8*. Callen JP. Clinically relevant information about cutaneous lupus erythematosus. Arch Dermatol. 2009; 145:316–319. Excellent overview of current clinical research issues related to cutaneous lupus. [PubMed: 19289766]

9*. Hemmati I, Otberg N, Martinka M, Alzolibani A, Restrepo I, Shapiro J. Discoid lupus erythematosus presenting with cysts, comedones, and cicatricial alopecia on the scalp. J Am Acad Dermatol. 2009; 60:1070–1072. Report that emphasizes the variation in presentations of discoid lupus. [PubMed: 19467382]

10**. Lehtinen DA, Harvey S, Mulcahy MJ, Hollis T, Perrino FW. The TREX1 double-stranded DNA degradation activity is defective in dominant mutations associated with autoimmune disease. J Biol Chem. 2008; 283:31649–31656. Studies that support a direct role for TREX1 in the degradation of dsDNA to prevent autoimmune disease. TREX1 mutations have been determined in familial chilblain lupus. [PubMed: 18805785]

11**. Nico MM, Vilela MA, Rivitti EA, Lourenco SV. Oral lesions in lupus erythematosus: correlation with cutaneous lesions. Eur J Dermatol. 2008; 18:376–381. Excellent overview of clinical and pathologic findings in oral lesions in lupus erythematosus, emphasizing the importance of differential diagnosis and lack of correlation with vasculitis. [PubMed: 18573706]

12*. Nuzum-Keim AD, Sontheimer RD. Ultraviolet light output of compact fluorescent lamps: comparison to conventional incandescent and halogen residential lighting sources. Lupus. 2009; 18:556–560. This study measures the output of different types of light bulbs and determines that compact fluorescent bulbs have less emission when covered. [PubMed: 19395458]

13*. Klein RS, Werth VP, Dowdy JC, Sayre RM. Analysis of compact fluorescent lights for use by patients with photosensitive conditions. Photochem Photobiol. 2009; 85:1004–1010. There are variable amounts of ultraviolet light emitted from compact fluorescent lights, a number of which are tested in this study. [PubMed: 19320850]

14*. Sontheimer RD, Henderson CL, Grau RH. Drug-induced subacute cutaneous lupus erythematosus: a paradigm for bedside-to-bench patient-oriented translational clinical investigation. Arch Dermatol Res. 2009; 301:65–70. Comprehensive review article about history and drugs implicated in drug-induced SCLE. [PubMed: 18797894]

15**. Bonilla-Martinez Z, Albrecht J, Taylor L, Okawa J, Werth VP. The CLASI is a useful clinical instrument to separately follow activity and damage during therapy of cutaneous lupus erythematosus. Arch Dermatol. 2008; 144:173. This is a study that demonstrates the responsiveness of the CLASI, an important study for extending validation of this index for measuring cutaneous lupus activity and damage. [PubMed: 18283174]

16**. Krathen MS, Dunham J, Gaines E, Grove G, Junkins-Hopkins J, Kim E, Kolasinksi SL, Kovarik C, Kwan-Morley J, Okawa J, Propert K, Rogers N, Rose M, Thomas P, Troxel A, Van Voorhees A, Von Feldt J, Weber AL, Werth VP. The Cutaneous Lupus Erythematosus Disease Activity and Severity Index (CLASI) expansion for rheumatology and dermatology. Arthr Care Res. 2008; 59:338–344. An important study that extends validation of the CLASI to rheumatologists.

17*. Kuhn A, Kuehn E, Meuth AM, Haust M, Nyberg F, Werth V, Ruzicka T, Schmitt V, Bonsmann G. Development of a Core Set Questionnaire by the European Society of Cutaneous Lupus Erythematosus (EUSCLE). Autoimmun Rev. 2009; 8:702–712. Development of a Core Set

Questionnaire for CLE for the European Society of Cutaneous Lupus Erythematosus. [PubMed: 19232553]

18**. Durosaro O, Davis MD, Reed KB, Rohlinger AL. Incidence of cutaneous lupus erythematosus, 1965–2005: a population-based study. Arch Dermatol. 2009; 145:249–253. This is the first population-based study related to the incidence of cutaneous lupus. [PubMed: 19289752]

19*. Moghadam-Kia S, Chilek K, Gaines E, Costner M, Rose ME, Okawa J, Werth VP. Cross-sectional analysis of a collaborative Web-based database for lupus erythematosus-associated skin lesions: prospective enrollment of 114 patients. Arch Dermatol. 2009; 145:255–260. This is the first systematic prospective study of the subtypes and severity of cutaneous lupus seen in an academic referral center. [PubMed: 19289753]

20*. Koskenmies S, Jarvinen TM, Onkamo P, Panelius J, Tuovinen U, Hasan T, Ranki A, Saarialho-Kere U. Clinical and laboratory characteristics of Finnish lupus erythematosus patients with cutaneous manifestations. Lupus. 2008; 17:337–347. Careful evaluation of 178 cutaneous lupus patients in terms of subsets, cluster analysis, laboratory findings, and increased smoking at disease onset relative to the general population. [PubMed: 18413417]

21. Popovic K, Wahren-Herlenius M, Nyberg F. Clinical follow-up of 102 anti-Ro/SSA-positive patients with dermatological manifestations. Acta Derm Venereol. 2008; 88:370–375. This is a study that reports development of a number of different autoimmune diseases in cohort of patients who are Ro/SSA-positive. [PubMed: 18709308]

22*. Sampaio MC, de Oliveira ZN, Machado MC, dos Reis VM, Vilela MA. Discoid lupus erythematosus in children--a retrospective study of 34 patients. Pediatr Dermatol. 2008; 25:163–167. This is a relatively large retrospective cohort of 34 children with discoid lupus. [PubMed: 18429771]

23**. Cusack C, Danby C, Fallon JC, Ho WL, Murray B, Brady J, O'Kelly P, Ambrose N, Kearns G, Murphy GM. Photoprotective behaviour and sunscreen use: impact on vitamin D levels in cutaneous lupus erythematosus. Photodermatol Photoimmunol Photomed. 2008; 24:260–267. This study examines the Vitamin D levels in 52 patients with cutaneous lupus determines that many have low vitamin D levels. [PubMed: 18811868]

24*. Tzellos TG, Kouvelas D. Topical tacrolimus and pimecrolimus in the treatment of cutaneous lupus erythematosus: an evidence-based evaluation. Eur J Clin Pharmacol. 2008; 64:337–341. This is a review of the five studies perfomed to evaluate the efficacy of topical macrolides for treatment of cutaneous lupus. [PubMed: 18157526]

25*. Kreuter A, Gaifullina R, Tigges C, Kirschke J, Altmeyer P, Gambichler T. Lupus erythematosus tumidus: response to antimalarial treatment in 36 patients with emphasis on smoking. Arch Dermatol. 2009; 145:244–248. This is a study that systematically evaluates the efficacy of antimalarials in tumid lupus, also demonstrating a decreased effect in smokers. [PubMed: 19289751]

26*. Shah A, Albrecht J, Bonilla-Martinez Z, Okawa J, Rose M, Rosenbach M, Werth V. Lenalidomide for the Treatment of Resistant Discoid Lupus Erythematosus, Arch Dermatol. Arch Dermatol. 2009; 145:303–306. Report of two cases of resistant discoid lupus treated with the thalidomide derivative lenalidomide, one of whom partially improved. [PubMed: 19289762]

27*. Erceg A, Bovenschen HJ, van de Kerkhof PC, de Jong EM, Seyger MM. Efficacy and safety of pulsed dye laser treatment for cutaneous discoid lupus erythematosus. J Am Acad Dermatol. 2009; 60:626–632. Report of the efficacy of pulsed dye laser for treatment of resistant lesions of cutaneous lupus. [PubMed: 19293010]

28*. Zara G, Ermani M, Rondinone R, Arienti S, Doria A. Thalidomide and sensory neurotoxicity: a neurophysiological study. J Neurol Neurosurg Psychiatry. 2008; 79:1258–1261. This study documents the high incidence of peripheral neuropathy in lupus patients treated with thalidomide. [PubMed: 18450790]

29*. Smith ES, Hallman JR, DeLuca AM, Goldenberg G, Jorizzo JL, Sangueza OP. Dermatomyositis: a clinicopathological study of 40 patients. Am J Dermatopathol. 2009; 31:61–67. This study demonstrates that skin biopsies of cutaneous lupus and dermatomyositis can not be differentiated. [PubMed: 19155727]

30*. Seidler AM, Gottlieb AB. Dermatomyositis induced by drug therapy: a review of case reports. J Am Acad Dermatol. 2008; 59:872–880. This review discusses medications associated with onset of dermatomyositis. [PubMed: 18625537]

31*. Dourmishev LA, Dourmishev AL. Activity of certain drugs in inducing of inflammatory myopathies with cutaneous manifestations. Expert Opin Drug Saf. 2008; 7:421–433. This is a review of drugs that can induce dermatomyositis. [PubMed: 18613806]

32*. Somani AK, Swick AR, Cooper KD, McCormick TS. Severe dermatomyositis triggered by interferon beta-1a therapy and associated with enhanced type I interferon signaling. Arch Dermatol. 2008; 144:1341–1349. This is a report of interferon beta for multiple sclerosis inducing dermatomyositis. [PubMed: 18936398]

33*. Dastmalchi M, Grundtman C, Alexanderson H, Mavragani CP, Einarsdottir H, Helmers SB, Elvin K, Crow MK, Nennesmo I, Lundberg IE. A high incidence of disease flares in an open pilot study of infliximab in patients with refractory inflammatory myopathies. Ann Rheum Dis. 2008; 67:1670–1677. This is a small open label study demonstrating a lack of efficacy of infliximab in patients with dermatomyositis, with several patients demonstrating a flare of skin disease. [PubMed: 18272672]

34*. Klein RQ, Bangert CC, Costner M, Connolly MK, Tanikawa EA, Okawa J, Rose M, Fakharzadeh SS, Fiorentino D, Lee LA, Sontheimer RD, Taylor L, Troxel AB, Werth VP. Comparison of the reliability and validity of outcome instruments for cutaneous dermatomyositis. Br J Dermatol. 2008; 159:887–894. This is a study that compares three outcome measures for skin findings of dermatomyositis, including the CDASI, CAT, and DSSI. [PubMed: 18616782]

35*. Huber AM, Lachenbruch PA, Dugan EM, Miller FW, Rider LG. Alternative scoring of the Cutaneous Assessment Tool in juvenile dermatomyositis: results using abbreviated formats. Arthritis Rheum. 2008; 59:352–356. Study that partially validates an abbreviated form of the Cutaneous Assessment Tool for juvenile dermatomyositis. [PubMed: 18311761]

36. Steen VD, Medsger TA Jr. Improvement in skin thickening in systemic sclerosis associated with improved survival. Arthritis Rheum. 2001; 44:2828–2835. [PubMed: 11762943]

37. Clements PJ, Hurwitz EL, Wong WK, Seibold JR, Mayes M, White B, Wigley F, Weisman M, Barr W, Moreland L, Medsger TA Jr, Steen VD, Martin RW, Collier D, Weinstein A, Lally E, Varga J, Weiner SR, Andrews B, Abeles M, Furst DE. Skin thickness score as a predictor and correlate of outcome in systemic sclerosis: high-dose versus low-dose penicillamine trial. Arthritis Rheum. 2000; 43:2445–2454. [PubMed: 11083267]

38. Perera A, Fertig N, Lucas M, Rodriguez-Reyna TS, Hu P, Steen VD, Medsger TA Jr. Clinical subsets, skin thickness progression rate, and serum antibody levels in systemic sclerosis patients with anti-topoisomerase I antibody. Arthritis Rheum. 2007; 56:2740–2746. [PubMed: 17665460]

39. Shand L, Lunt M, Nihtyanova S, Hoseini M, Silman A, Black CM, Denton CP. Relationship between change in skin score and disease outcome in diffuse cutaneous systemic sclerosis: application of a latent linear trajectory model. Arthritis Rheum. 2007; 56:2422–2431. [PubMed: 17599771]

40**. Hanitsch LG, Burmester GR, Witt C, Hunzelmann N, Genth E, Krieg T, Lehmacher W, Melchers I, Meurer M, Muller-Ladner U, Schulze-Lohoff E, Becker M, Sunderkoetter C, Riemekasten G. Skin sclerosis is only of limited value to identify SSc patients with severe manifestations--an analysis of a distinct patient subgroup of the German Systemic Sclerosis Network (DNSS) Register. Rheumatology (Oxford). 2009; 48:70–73. This analysis of 1200 patients with systemic sclerosis demonstrated that higher modified Rodnan skin scores are associated with dysphagia, reflux, pulmonary fibrosis, contractures, and digital ulcers but not other disease manifestations, and that patients with mild skin disease are still at risk of severe systemic manifestations. [PubMed: 19056798]

41. Furst D, Khanna D, Matucci-Cerinic M, Clements P, Steen V, Pope J, Merkel P, Foeldvari I, Seibold J, Pittrow D, Polisson R, Strand V. Systemic sclerosis - continuing progress in developing clinical measures of response. J Rheumatol. 2007; 34:1194–1200. [PubMed: 17477486]

42. Czirjak L, Nagy Z, Aringer M, Riemekasten G, Matucci-Cerinic M, Furst DE. The EUSTAR model for teaching and implementing the modified Rodnan skin score in systemic sclerosis. Ann Rheum Dis. 2007; 66:966–969. [PubMed: 17234649]

43. Czirjak L, Foeldvari I, Muller-Ladner U. Skin involvement in systemic sclerosis. Rheumatology (Oxford). 2008; 47 (Suppl 5):v44–45. [PubMed: 18784142]

44. Gazi H, Pope JE, Clements P, Medsger TA, Martin RW, Merkel PA, Kahaleh B, Wollheim FA, Baron M, Csuka ME, Emery P, Belch JF, Hayat S, Lally EV, Korn JH, Czirjak L, Herrick A, Voskuyl AE, Bruehlmann P, Inanc M, Furst DE, Black C, Ellman MH, Moreland LW, Rothfield NF, Hsu V, Mayes M, McKown KM, Krieg T, Siebold JR. Outcome measurements in scleroderma: results from a delphi exercise. J Rheumatol. 2007; 34:501–509. [PubMed: 17299843]

45. Morita A, Kobayashi K, Isomura I, Tsuji T, Krutmann J. Ultraviolet A1 (340–400 nm) phototherapy for scleroderma in systemic sclerosis. J Am Acad Dermatol. 2000; 43:670–674. [PubMed: 11004624]

46. Sakakibara N, Sugano S, Morita A. Ultrastructural changes induced in cutaneous collagen by ultraviolet-A1 and psoralen plus ultraviolet A therapy in systemic sclerosis. J Dermatol. 2008; 35:63–69. [PubMed: 18271800]

47*. Rose RF, Turner D, Goodfield MJ, Goulden V. Low-dose UVA1 phototherapy for proximal and acral scleroderma in systemic sclerosis. Photodermatol Photoimmunol Photomed. 2009; 25:153–155. This retrospective study is one of the few documenting the generally accepeted effectiveness of phototherapy for cutaneous sclerosis in diffuse and localized scleroderma. [PubMed: 19438995]

48. Derk CT, Huaman G, Jimenez SA. A retrospective randomly selected cohort study of D-penicillamine treatment in rapidly progressive diffuse cutaneous systemic sclerosis of recent onset. Br J Dermatol. 2008; 158:1063–1068. [PubMed: 18284395]

49. Clements PJ, Furst DE, Wong WK, Mayes M, White B, Wigley F, Weisman MH, Barr W, Moreland LW, Medsger TA Jr, Steen V, Martin RW, Collier D, Weinstein A, Lally E, Varga J, Weiner S, Andrews B, Abeles M, Seibold JR. High-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis: analysis of a two-year, double-blind, randomized, controlled clinical trial. Arthritis Rheum. 1999; 42:1194–1203. [PubMed: 10366112]

50. Vanthuyne M, Blockmans D, Westhovens R, Roufosse F, Cogan E, Coche E, Nzeusseu Toukap A, Depresseux G, Houssiau FA. A pilot study of mycophenolate mofetil combined to intravenous methylprednisolone pulses and oral low-dose glucocorticoids in severe early systemic sclerosis. Clin Exp Rheumatol. 2007; 25:287–292. [PubMed: 17543155]

51. Daoussis D, Liossis SN, Tsamandas AC, Kalogeropoulou C, Kazantzi A, Sirinian C, Karampetsou M, Yiannopoulos G, Andonopoulos AP. Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. Rheumatology (Oxford). 2009

52. Lafyatis R, Kissin E, York M, Farina G, Viger K, Fritzler MJ, Merkel PA, Simms RW. B cell depletion with rituximab in patients with diffuse cutaneous systemic sclerosis. Arthritis Rheum. 2009; 60:578–583. [PubMed: 19180481]

53. Khanna D, Clements PJ, Furst DE, Korn JH, Ellman M, Rothfield N, Wigley FM, Moreland LW, Silver R, Kim YH, Steen VD, Firestein GS, Kavanaugh AF, Weisman M, Mayes MD, Collier D, Csuka ME, Simms R, Merkel PA, Medsger TA Jr, Sanders ME, Maranian P, Seibold JR. Recombinant human relaxin in the treatment of systemic sclerosis with diffuse cutaneous involvement: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2009; 60:1102–1111. [PubMed: 19333948]

54. Denton CP, Merkel PA, Furst DE, Khanna D, Emery P, Hsu VM, Silliman N, Streisand J, Powell J, Akesson A, Coppock J, Hoogen F, Herrick A, Mayes MD, Veale D, Haas J, Ledbetter S, Korn JH, Black CM, Seibold JR. Recombinant human anti-transforming growth factor beta1 antibody therapy in systemic sclerosis: a multicenter, randomized, placebo-controlled phase I/II trial of CAT-192. Arthritis Rheum. 2007; 56:323–333. [PubMed: 17195236]

55*. Kawald A, Burmester GR, Huscher D, Sunderkotter C, Riemekasten G. Low versus high-dose iloprost therapy over 21 days in patients with secondary Raynaud's phenomenon and systemic sclerosis: a randomized, open, single-center study. J Rheumatol. 2008; 35:1830–1837. This prospective, open-label, randomized trial demonstrates the equivalent efficacy of low and high-dose iloprost for severe Raynaud's phenomenon. [PubMed: 18634152]

56. Sebastiani M, Manfredi A, Colaci M, D'Amico R, Malagoli V, Giuggioli D, Ferri C. Capillaroscopic skin ulcer risk index: a new prognostic tool for digital skin ulcer development in systemic sclerosis patients. Arthritis Rheum. 2009; 61:688–694. [PubMed: 19405007]

57. Hemmatazad H, Rodrigues HM, Maurer B, Brentano F, Pileckyte M, Distler JH, Gay RE, Michel BA, Gay S, Huber LC, Distler O, Jungel A. Histone deacetylase 7, a potential target for the antifibrotic treatment of systemic sclerosis. Arthritis Rheum. 2009; 60:1519–1529. [PubMed: 19404935]

58. Ikawa Y, Ng PS, Endo K, Kondo M, Chujo S, Ishida W, Shirasaki F, Fujimoto M, Takehara K. Neutralizing monoclonal antibody to human connective tissue growth factor ameliorates transforming growth factor-beta-induced mouse fibrosis. J Cell Physiol. 2008; 216:680–687. [PubMed: 18481257]

59**. Chung L, Fiorentino DF, Benbarak MJ, Adler AS, Mariano MM, Paniagua RT, Milano A, Connolly MK, Ratiner BD, Wiskocil RL, Whitfield ML, Chang HY, Robinson WH. Molecular framework for response to imatinib mesylate in systemic sclerosis. Arthritis Rheum. 2009; 60:584–591. This is one of the first studies demonstrating clinical efficacy of imatinib mesylate in two patients with diffuse cutaneous systemic sclerosis. The results of immunohistochemical analyses of skin biopsy specimens and gene expression profiling in these patients suggested that PDGFRβ and Abl play critical, synergistic roles in the pathogenesis of SSc, and that imatinib targets a gene expression program that is frequently dysregulated in dcSSc. [PubMed: 19180499]

60. Distler JH, Jungel A, Huber LC, Schulze-Horsel U, Zwerina J, Gay RE, Michel BA, Hauser T, Schett G, Gay S, Distler O. Imatinib mesylate reduces production of extracellular matrix and prevents development of experimental dermal fibrosis. Arthritis Rheum. 2007; 56:311–322. [PubMed: 17195235]

61. Rozin A, Yigla M, Guralnik L, Keidar Z, Vlodavsky E, Rozenbaum M, Nahir AM, Balbir-Gurman A. Rheumatoid lung nodulosis and osteopathy associated with leflunomide therapy. Clin Rheumatol. 2006; 25:384–388. [PubMed: 16211338]

62. Chao J, Parker BA, Zvaifler NJ. Accelerated cutaneous nodulosis associated with aromatase inhibitor therapy in a patient with rheumatoid arthritis. J Rheumatol. 2009; 36:1087–1088. [PubMed: 19435976]

63. Sayah A, English JC. Rheumatoid arthritis: a review of the cutaneous manifestations. J Am Acad Dermatol. 2005; 53:191. [PubMed: 16021111]

64**. Turesson C, Matteson EL. Vasculitis in rheumatoid arthritis. Curr Opin Rheumatol. 2009; 21:35–40. This recent review explores the pathophysiology, epidemiology, clinical features, and therapeutic options related to rheumatoid vasculitis. [PubMed: 19077716]

65. Puechal X, Miceli-Richard C, Mejjad O, Lafforgue P, Marcelli C, Solau-Gervais E, Steinfeld S, Villoutreix C, Treves R, Mariette X, Guillevin L. Anti-tumour necrosis factor treatment in patients with refractory systemic vasculitis associated with rheumatoid arthritis. Ann Rheum Dis. 2008; 67:880–884. [PubMed: 18037625]

66. Kawakami T, Yamazaki M, Kawasaki K, Mizoguchi M, Soma Y. Therapeutic effect of argatroban on rheumatoid vasculitis with antiphosphatidylserine-prothrombin complex antibody. Arch Dermatol. 2008; 144:1075–1076. [PubMed: 18711097]

67. Chu P, Connolly MK, LeBoit PE. The histopathologic spectrum of palisaded neutrophilic and granulomatous dermatitis in patients with collagen vascular disease. Arch Dermatol. 1994; 130:1278. [PubMed: 7944509]

68. Kawachi Y, Nakamura Y, Yoh K, Suzuki T, Fujisawa Y, Furuta J, Takahashi T, Otsuka F. Rheumatoid papules successfully treated with oral tacrolimus. J Eur Acad Dermatol Venereol. 2008; 22:241–242. [PubMed: 18211423]

69. Kreuter A, Gambichler T, Altmeyer P. Infliximab therapy for interstitial granulomatous dermatitis. J Eur Acad Dermatol Venereol. 2007; 21:251–252. [PubMed: 17243965]

70. Hu S, Cohen D, Murphy G, Mody E, Qureshi AA. Interstitial granulomatous dermatitis in a patient with rheumatoid arthritis on etanercept. Cutis. 2008; 81:336–338. [PubMed: 18491481]

71. Deng A, Harvey V, Sina B, Strobel D, Badros A, Junkins-Hopkins JM, Samuels A, Oghilikhan M, Gaspari A. Interstitial granulomatous dermatitis associated with the use of tumor necrosis factor alpha inhibitors. Arch Dermatol. 2006; 142:198–202. [PubMed: 16490847]

72. Fiorentino DF. The Yin and Yang of TNF-alpha inhibition. Arch Dermatol. 2007; 143:233–236. [PubMed: 17310003]

73. Wollina U, Hansel G, Koch A, Schonlebe J, Kostler E, Haroske G. Tumor necrosis factor-alpha inhibitor-induced psoriasis or psoriasiform exanthemata: first 120 cases from the literature including a series of six new patients. Am J Clin Dermatol. 2008; 9:1–14. [PubMed: 18092839]

74. de Gannes GC, Ghoreishi M, Pope J, Russell A, Bell D, Adams S, Shojania K, Martinka M, Dutz JP. Psoriasis and pustular dermatitis triggered by TNF-alpha inhibitors in patients with rheumatologic conditions. Arch Dermatol. 2007; 143:223–231. This study provides insight into the pathomechanisms of psoriasiform reactions to TNFα inhibition. [PubMed: 17310002]