Expert Review of Dermatology

ISSN: 1746-9872 (Print) 1746-9880 (Online) Journal homepage: informahealthcare.com/journals/ierg20

Sclerotic skin disease: when smooth skin is unwelcome

Audrey W Tan & Jan P Dutz

To cite this article: Audrey W Tan & Jan P Dutz (2006) Sclerotic skin disease: when smooth skin is unwelcome, Expert Review of Dermatology, 1:4, 487-492, DOI: 10.1586/17469872.1.4.487

To link to this article: https://doi.org/10.1586/17469872.1.4.487

Published online: 10 Jan 2014.

Audrey W Tan [†] ***and Jan P Dutz***
[†]*Author for correspondence*
Department of Dermatology and Skin Sciences, University of British Columbia, Vancouver BC, Canada; National Skin Centre, 1 Mandalay Road, Singapore, 308205
Tel.: +65 6253 4455
Fax: +65 6253 3225
audreytan@nsc.gov.sg

Sclerotic skin disease: when smooth skin is unwelcome

'Dermatologists can participate in the holistic care of patients by aiding in early diagnosis and contributing to the management of specific cutaneous complications.'

Expert Rev. Dermatol. 1(4), 487–492 (2006)

Localized scleroderma (LS) and progressive systemic sclerosis (SSc) are debilitating and potentially fatal sclerotic skin diseases with uncertain etiology. How vascular alterations, inflammation and autoimmunity, and fibrosis interact in the pathophysiological triangle of the sclerodermas is not completely understood. Extensive research has been rewarded by therapeutic strategies that have led to decreased morbidity and a better quality of life for patients. With sustained interest and continuing research efforts, we are hopeful that further promising treatments will emerge.

Sclerotic skin disease: when smooth skin is unwelcome

Scleroderma is derived from the Greek term skleros (hard) and derma (skin). Sclerotic skin disorders are an intriguing group of diseases, with incompletely understood pathogenetic complexities and ongoing therapeutic challenges. They are important to recognize as they can be associated with significant morbidity and occasional mortality. Primary cutaneous sclerosis encompasses morphea or LS and SSc. Nonimmune or secondary cutaneous sclerosis may be associated with drugs such as bleomycin and pentazocine, exposure to chemicals such as polyvinyl chloride, metabolic disorders including porphyria cutanea tarda and nephrogenic fibrosing dermopathy, genetic disorders or malignancy.

Localized scleroderma

LS is characterized by limited inflammatory sclerosis and fibrosis of the skin and adjacent subcutis. In contrast to SSc, Raynaud's phenomenon (RP), acrosclerosis and internal organ involvement do not usually occur. LS may be classified under five subtypes: plaque, generalized, bullous, linear or deep morphea [1]. In one pediatric series, 15% of patients had a mixed subtype [2]. The different types of LS are similar in the elements of the histopathological findings, but differ with regard to severity and depth of involvement. The histopathological differentiation between LS and SSc is not always possible. In a histopathological study, inflammatory changes were more prominent in LS than in SSc, and sclerosis of the papillary dermis was frequently seen in LS but absent in SSc [3]. The simultaneous involvement of the superficial dermis with deep dermal changes may help in differentiating LS from SSc.

Etiopathogenesis

The cause of LS or SSc remains unknown. LS has been reported after trauma [4], tetanus vaccination [5], ischemic injury [6], radiation [7] and at sites of venous insufficiency [8]. LS and SSc may potentially be associated with occupational toxic factors, including organic solvents, epoxy resins and silica [9,10]. Weide and colleagues summarized studies that have attempted to detect *Borrelia burgdorferi* in lesional skin of patients with morphea using histological and immunohistological methods, cultivation of the spirochete from tissue sections, PCR or serological methods [11]. It appears that *B. burgdorferi* may be implicated in the pathogenesis of at least some cases of morphea in Europe and Asia [12,13], but almost certainly not in the USA [13,14].

10.1586/17469872.1.4.487

ISSN 1746-9872

Prognosis

The historical concept that LS differs from SSc in that pathology in the former is confined to the skin and confers a relatively benign course, has been challenged by recent data from a large series of 750 children with juvenile LS where 22.4% of these children were found to have extracutaneous manifestations of LS. The risk of patients with juvenile LS and extracutaneous manifestations developing SSc was low (0.13%), but the disease appeared to be more severe in these patients than those with skin involvement only [2]. These findings raise the issue of how extensively children, and perhaps adults with LS, should be evaluated and monitored for internal organ involvement, particularly the joints, eyes and CNS.

Immunological abnormalities

Autoantibodies are common in LS, underlining the systemic nature of the disease process [15]. Recent studies have identified serum autoantibodies to fibrillin-1 in LS [16] and SSc [17]. Fibrillin-1 is the major component of the extracellular matrix found in skin and other connective tissue. No correlations have been found between antifibrillin-1 antibodies and skin disease activity or antinuclear antibody positivity in patients with LS. Rheumatoid factors are well described in LS [18]. Serum levels of antiagalactosyl (anti-AG) immunoglobulin (Ig)G antibodies, denoting a specificity commonly found in rheumatoid factors, have also been found to be significantly higher in patients with LS than in healthy controls [19]. A correlation between the number of sclerotic lesions or involved areas with anti-AG IgG levels suggest that serum anti-AG IgG levels may be a useful marker in determining the severity of LS. Interestingly, plasma cells and immature plasma cells have long been known to contribute to the cellular infiltrate in morphea, although their pathophysiological role remains unclear [20].

'Extensive research has been rewarded by therapeutic strategies that have led to decreased morbidity and a better quality of life for patients.'

Therapy

There is no uniformly effective or accepted therapy for LS. Phototherapy and photochemotherapy have become important treatment options for sclerotic skin diseases. Overall, long-wave UVA (UVA1) appears more efficacious followed by psoralen plus UVA (PUVA) with either topical or systemic psoralens. The mechanism of action of UVA in sclerotic skin disease appears to involve the local induction of collagenase production by fibroblasts [21]. It has been shown that increased collagenase expression in irradiated plaques of morphoea accompanies improvement with UVA1 phototherapy [22]. As PUVA increases the risk of cutaneous malignancy and long-wave UVA sources are expensive and in limited supply, broadband UVA can be considered as an alternative therapeutic modality in both LS and SSc [23]. In a randomized controlled trial comparing the safety and efficacy of low-dose UVA1 (20 J/cm^2), medium-dose UVA1 (50 J/cm^2) and narrowband UVB (NBUVB) in the treatment of LS, medium-dose UVA1 was significantly more effective than NBUVB and low-dose UVA1 was as effective as NBUVB [24]. Combined therapy with calcipotriol ointment and low-dose UVA1 phototherapy has also been reported to be highly effective in childhood morphea [25]. Further controlled (and preferably blinded) studies are still necessary to confirm the benefit of these phototherapeutic modalities.

For generalized, aggressive disease, UVA treatment modalities, systemic corticosteroids or methotrexate may be contemplated. Methotrexate (with or without oral corticosteroids) was shown in a recent series to be effective and safe in 17 pediatric patients with LS who failed topical therapy [26]. In a study of severe LS, 13 out of 15 patients treated with oral methotrexate combined with pulsed intravenous methylprednisolone for a mean duration of 9.8 months had significant improvement in clinical scores and histological and ultrasonographic assessments [27]. There were no serious adverse effects.

Progressive systemic sclerosis

Progressive SSc is a multisystem disease, characterized by distal and proximal extremity and truncal skin thickening. In diffuse cutaneous SSc (dcSSc), sclerosis occurs proximal to the neck, elbows or knees, and interstitial lung disease, renal and cardiac involvement may occur. In limited cutaneous SSc (lcSSc; previously calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia [CREST] syndrome), sclerosis involves distal sites only and pulmonary hypertension and small bowel malabsorption are potential severe complications. The term systemic sclerosis sine scleroderma is applied to individuals who have serological or vascular features of SSc but who lack definite skin sclerosis. Scleroderma overlap syndromes include mixed connective tissue disease, scleromyositis (associated with anti-PM-Scl antibodies) and the synthetase syndrome (associated with anti-Jo-1 antibodies).

Etiopathogenesis

Three main themes have evolved from studies on the pathophysiology of both LS and SSc: vascular damage, immune system activation and inflammation, and altered collagen metabolism [28]. Other mechanisms, such as apoptosis of endothelial cells and oxidative stress with overproduction of reactive oxygen species, are also speculated to be involved in the induction of scleroderma [29]. The finding of increased prevalence of human parvovirus B19 DNA in SSc skin [30], and the demonstration of parvovirus B19 DNA in bone marrow biopsies of SSc patients [31], suggest that the virus may be involved in the pathogenesis of SSc. Genetic factors possibly play a role. The Amerindian human leukocyte antigen haplotype appears to be a risk factor for disease

development [32], and a gene haplotype of the gene for fibrillin-1 is seen in increased frequency in the Choctaw Indians [33]. Interestingly, abnormal fibrillin-1 expression has recently been associated with excessive transforming growth factor (TGF)-β signaling [34]. A study investigating racial variation demonstrated that black people experienced an earlier age of disease onset than white people, and were significantly more likely to have diffuse disease, digital ulcers, digital pitting and impaired lung function [35].

Autoantibody profiles

Autoantibody profiles within the scleroderma disease spectrum associate with disease phenotype and are important diagnostic and prognostic markers [36]. For example, patients with the anticentromere antibody are not likely to develop diffuse cutaneous disease and demonstrate a lower frequency of pulmonary fibrosis [36]. They do, however, need to be carefully monitored for the development of pulmonary hypertension, as this is the major cause of death in these patients.

Prognosis

A review of the US national mortality rate for SSc over a 20-year observation period revealed a mortality rate of 3.9 per million [37]. The risk of developing and dying from severe organ complications in SSc is highest within the first 5 years of the disease. A study involving 953 patients with SSc revealed that patients with only severe skin thickening and no other severe organ damage had a cumulative 9-year survival rate of 72%, which was significantly and dramatically better than 38% for those with any severe organ involvement [38]. Approximately 50% of scleroderma-related deaths are a result of pulmonary disease, whilst renal disease accounts for another 7–10% [39]. Mortality from scleroderma renal crisis has fallen significantly following the advent of angiotensin-converting enzyme inhibitors. Patients at high risk for pulmonary or renal complications should be identified and closely monitored [39,40].

'Although intense research has led to significant advances in therapies directed at pathogenetic mechanisms and end-organ complications, optimal therapeutic strategies remain a challenge.'

Management of skin disease

Although treatment of SSc is difficult, there have been substantial advances in the treatment of individual organ-based complications, resulting in improvement in morbidity and quality of life. Treatment is targeted at the pathogenic pathways causing variable damage in individual organs and is focused on vascular, immunological and antifibrotic therapies. General measures, including protection against cold and trauma, and active and passive physiotherapy, should not be overlooked.

Raynaud's phenomenon & digital ulcers

Calcium channel antagonists remain the primary therapeutic modality for RP. A meta-analysis of the efficacy of calcium channel blockers for the treatment of RP in SSc showed that calcium channel blockers resulted in a mean reduction of 8.3 attacks in 2 weeks, and reduction in severity of 35% [41]. The angiotensin II receptor type 1 antagonist, losartan, has been shown to result in symptomatic improvement in both primary RP and RP secondary to SSc [42]. Intravenous iloprost, a prostacyclin antagonist, is another effective agent in the treatment of RP secondary to SSc, decreasing the frequency and severity of attacks, as well as improving quality of life [43]. A preliminary report suggests that statins may enhance deficient circulating endothelial cell precursors in SSc and improve RP [44]. Bosentan is an endothelin-1 antagonist effective in the treatment of idiopathic and scleroderma-associated pulmonary hypertension. It has been shown in a multicenter, placebo-controlled trial that bosentan is effective in preventing the development of digital ulcers in patients with SSc [45]. Data from a retrospective analysis suggests that bosentan may also promote healing of active ischemic digital ulcers [46], although this has not been confirmed prospectively [47].

Calcinosis

Several therapeutic modalities have been attempted with variable success and include low-dose warfarin, colchicine, bisphosphonates, calcium antagonists, probenecid, surgical excision and carbon dioxide laser therapy [48]. Minocycline in doses of 50 or 100 mg daily may be beneficial in decreasing the frequency of ulceration and inflammation associated with cutaneous calcinosis, as well as reducing the size of calcium deposits [49].

Fibrosis

In a study of 18 patients with SSc, low-dose UVA1 (30 J/cm^2 per exposure for 50 sessions) therapy of the hands resulted in increased skin elasticity, decreased skin thickness, improved finger mobility and an increase in collagenase [50]. Maintenance of clinical improvement was not assessed in this study. TGF-β is a key mediator in fibrosis and has been postulated to play a role in the pathogenesis of scleroderma [29]. Studies in mouse models of bleomycin-induced scleroderma have demonstrated that blockade of TGF-β by antibodies to TGF-β resulted in a reduction in cutaneous sclerosis [51]. Targeting TGF-β signaling may therefore be a potential therapeutic approach in ameliorating fibrosis in SSc and developments in this field are ongoing.

Extracorporeal photochemotherapy (ECP) may be a promising modality for the treatment of cutaneous disease in SSc. In a placebo-controlled trial, skin thickness and joint involvement improved within 6 months of photophoresis when compared with baseline values [52]. It has been proposed that ECP induces the release of various cytokines by phototreated monocytes, including interferon-γ and tumor necrosis factor-α, activating collagen degradation and decreasing collagen synthesis [53].

Immunosuppressive therapy

Evidence for the involvement of cellular and humoral immunity in the pathogenesis of SSc has led to the use of various immunosuppressive agents as potential disease-modifying therapies. The effects of intensive immunosuppressive and anti-inflammatory therapy are, however, disappointing when compared with other rheumatic diseases. For example, methotrexate as a treatment for cutaneous disease in SSc has produced mixed results in two placebo-controlled studies, one demonstrating improvements in skin scores and hand-grip strength in treated patients [54], the other favoring methotrexate but failing to reach significance in several key outcome measures [55], possibly due to lower treatment dosages.

Autologous stem cell transplantation

Uncontrolled trials have suggested that immunosuppressive therapy followed by autologous stem cell transplantation may result in complete or partial remission of disease in some patients (including resolution of dermal sclerosis), but concerns surrounding transplant-related morbidity and mortality remain [56–58]. There are ongoing multicenter trials examining the safety and efficacy of high-dose immunosuppressive treatment and autologous stem cell transplantation versus conventional chemotherapy in patients with severe SSc at risk of mortality from organ failure [59].

Conclusion

There remain unanswered questions regarding the etiology of the sclerodermas and disease pathogenesis is only partially understood. Although intense research has led to significant advances in therapies directed at pathogenetic mechanisms and end-organ complications, optimal therapeutic strategies remain a challenge. Do dermatologists have a role in the management of this group of diseases? Dermatologists can participate in the holistic care of patients by aiding in early diagnosis and contributing to the management of specific cutaneous complications, as well as to the prompt detection of other organ involvement. Dermatologists can also facilitate entry of appropriate patients into ongoing clinical trials, which will hopefully provide us with new data regarding therapeutic approaches, ultimately leading to more effective disease-modifying therapy in the near future.

References

1 Peterson LS, Nelson AM, Su WP. Classification of morphea (localized scleroderma). *Mayo Clin. Proc.* 70(11), 1068–1076 (1995).

2 Zulian F, Athreya BH, Laxer R *et al.* Juvenile localized scleroderma: clinical and epidemiological features in 750 children. An international study. *Rheumatology (Oxford)* 45(5), 614–620 (2006).

3 Torres JE, Sanchez JL. Histopathologic differentiation between localized and systemic scleroderma. *Am. J. Dermatopathol.* 20(3), 242–245 (1998).

4 Yamanaka CT, Gibbs NF. Trauma-induced linear scleroderma. *Cutis* 63(1), 29–32 (1999).

5 Drago F, Rampini P, Lugani C, Rebora A. Generalized morphoea after antitetanus vaccination. *Clin. Exp. Dermatol.* 23(3), 142 (1998).

6 McColl G, Buchanan RR. Unilateral scleroderma following ischemic hand injury. *J. Rheumatol.* 21(2), 380–381 (1994).

7 Schaffer JV, Carroll C, Dvoretsky I, Huether MJ, Girardi M. Postirradiation morphea of the breast: presentation of two cases and review of the literature. *Dermatology* 200(1), 67–71 (2000).

8 Ludwig RJ, Werner RJ, Winker W, Boehncke WH, Wolter M, Kaufmann R. Chronic venous insufficiency – a potential trigger for localized scleroderma. *J. Eur. Acad. Dermatol. Venereol.* 20(1), 96–99 (2006).

9 Magnant J, de Monte M, Guilmot JL *et al.* Relationship between occupational risk factors and severity markers of systemic sclerosis. *J. Rheumatol.* 32(9), 1713–1718 (2005).

10 Bovenzi M, Barbone F, Pisa FE, *et al.* A case-control study of occupational exposures and systemic sclerosis. *Int. Arch. Occup. Environ. Health* 77(1), 10–16 (2004).

11 Weide B, Walz T, Garbe C. Is morphoea caused by *Borrelia burgdorferi*? A review. *Br. J. Dermatol.* 142(4), 636–644 (2000).

12 Breier FH, Aberer E, Stanek G, Khanakaha G, Schlick A, Tappeiner G. Isolation of *Borrelia afzelii* from circumscribed scleroderma. *Br. J. Dermatol.* 140(5), 925–930 (1999).

13 Fujiwara H, Fujiwara K, Hashimoto K *et al.* Detection of *Borrelia burgdorferi* DNA (*B. garinii* or *B. afzelii*) in morphea and lichen sclerosus et atrophicus tissues of German and Japanese but not of US patients. *Arch. Dermatol.* 133(1), 41–44 (1997).

14 Dillon WI, Saed GM, Fivenson DP. *Borrelia burgdorferi* DNA is undetectable by polymerase chain reaction in skin lesions of morphea, scleroderma, or lichen sclerosus et atrophicus of patients from North America. *J. Am. Acad. Dermatol.* 33(4), 617–620 (1995).

15 Takehara K, Sato S. Localized scleroderma is an autoimmune disorder. *Rheumatology (Oxford)* 44(3), 274–279 (2005).

16 Arnett FC, Tan FK, Uziel Y *et al.* Autoantibodies to the extracellular matrix microfibrillar protein, fibrillin 1, in patients with localized scleroderma. *Arthritis Rheum.* 42(12), 2656–2659 (1999).

17 Tan FK, Arnett FC, Antohi S *et al.* Autoantibodies to the extracellular matrix microfibrillar protein, fibrillin-1, in patients with scleroderma and other connective tissue diseases. *J. Immunol.* 163(2), 1066–1072 (1999).

18 Mimura Y, Ihn H, Jinnin M, Asano Y, Yamane K, Tamaki K. Rheumatoid factor isotypes in localized scleroderma. *Clin. Exp. Dermatol.* 30(4), 405–408 (2005).

19 Mimra Y, Ihn H, Jinnin M *et al.* Anti-agalactosyl immunoglobulin G antibodies in localized scleroderma. *Int. J. Dermatol.* 44(10), 817–820 (2005).

20 Fleischmajer R, Perlish JS, Reeves JR. Cellular infiltrates in scleroderma skin. *Arthritis Rheum.* 20(4), 975–984 (1977).

21 Petersen MJ, Hansen C, Craig S. Ultraviolet A irradiation stimulates collagenase production in cultured human fibroblasts. *J. Invest. Dermatol.* 99(4), 440–444 (1992).

22 Stege H, Berneburg M, Humke S *et al.* High-dose UVA1 radiation therapy for localized scleroderma. *J. Am. Acad. Dermatol.* 36(6 Pt 1), 938–944 (1997).

23 El-Mofty M, Mostafa W, El-Darouty M *et al.* Different low doses of broad-band UVA in the treatment of morphea and systemic sclerosis. *Photodermatol. Photoimmunol. Photomed.* 20(3), 148–156 (2004).

24 Kreuter A, Hyun J, Stucker M, Sommer A, Altmeyer P, Gambichler T. A randomized controlled study of low-dose UVA1, medium-dose UVA1, and narrowband UVB phototherapy in the treatment of localized scleroderma. *J. Am. Acad. Dermatol.* 54(3), 440–447 (2006).

25 Kreuter A, Gambichler T, Avermaete A *et al*. Combined treatment with calcipotriol ointment and low-dose ultraviolet A1 phototherapy in childhood morphea. *Pediatr. Dermatol.* 18(3), 241–245 (2001).

26 Fitch PG, Rettig P, Burnham JM *et al*. Treatment of pediatric localized scleroderma with methotrexate. *J. Rheumatol.* 33(3), 609–614 (2006).

27 Kreuter A, Gambichler T, Breuckmann F *et al*. Pulsed high-dose corticosteroids combined with low-dose methotrexate in severe localized scleroderma. *Arch. Dermatol.* 141(7), 847–852 (2005).

28 Charles C, Clements P, Furst DE. Systemic sclerosis: hypothesis-driven treatment strategies. *Lancet* 367(9523), 1683–1691 (2006).

29 Yamamoto T. The bleomycin-induced scleroderma model: what have we learned for scleroderma pathogenesis? *Arch. Dermatol. Res.* 297(8), 333–344 (2006).

30 Ohtsuka T, Yamazaki S. Increased prevalence of human parvovirus B19 DNA in systemic sclerosis skin. *Br. J. Dermatol.* 150(6), 1091–1095 (2004).

31 Ferri C, Longombardo G, Azzi A, Zakrzewska K. Parvovirus B19 and systemic sclerosis. *Clin. Exp. Rheumatol.* 17(2), 267–268 (1999).

32 Arnett FC, Howard RF, Tan F *et al*. Increased prevalence of systemic sclerosis in a Native American tribe in Oklahoma. Association with an Amerindian HLA haplotype. *Arthritis Rheum.* 39(8), 1362–1370 (1996).

33 Tan FK, Stivers DN, Foster MW *et al*. Association of microsatellite markers near the fibrillin 1 gene on human chromosome 15q with scleroderma in a native American population. *Arthritis Rheum.* 41(10), 1729–1737 (1998).

34 Habashi JP, Judge DP, Holm TM *et al*. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. *Science* 312(5770), 117–121 (2006).

35 Nietert PJ, Mitchell HC, Bolster MB, Shaftman SR, Tilley BC, Silver RM. Racial variation in clinical and immunological manifestations of systemic sclerosis. *J. Rheumatol.* 33(2), 63–68 (2006).

36 Steen VD. Autoantibodies in systemic sclerosis. *Semin. Arthritis Rheum.* 35(1), 35–42 (2005).

37 Krishnan E, Furst DE. Systemic sclerosis mortality in the United States: 1979–1998. *Eur. J. Epidemiol.* 20(10), 855–861 (2005).

38 Steen VD, Medsger TA Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. *Arthritis Rheum.* 43(11), 2437–2444 (2000).

39 Steen VD. The lung in systemic sclerosis. *J Clin. Rheumatol.* 11(1), 40–46 (2005).

40 Steen V. Targeted therapy for systemic sclerosis. *Autoimmun. Rev.* 5(2), 122–124 (2006).

41 Thompson AE, Shea B, Welch V, Fenlon D, Pope JE. Calcium-channel blockers for Raynaud's phenomenon in systemic sclerosis. *Arthritis Rheum.* 44(8), 1841–1847 (2001).

42 Dziadzio M, Denton CP, Smith R *et al*. Losartan therapy for Raynaud's phenomenon and scleroderma: clinical and biochemical findings in a fifteen-week, randomized, parallel-group, controlled trial. *Arthritis Rheum.* 42(12), 2646–2655 (1999).

43 Milio G, Corrado E, Genova C *et al*. Iloprost treatment in patients with Raynaud's phenomenon secondary to systemic sclerosis and the quality of life: a new therapeutic protocol. *Rheumatology (Oxford)* 45(8), 999–1004 (2006).

44 Kuwana M, Kaburaki J, Okazaki Y, Yasuoka H, Kawakami Y, Ikeda Y. Increase in circulating endothelial precursors by atorvastatin in patients with systemic sclerosis. *Arthritis Rheum.* 54(6), 1946–1951 (2006).

45 Korn JH, Mayes M, Matucci Cerinic M *et al*. Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. *Arthritis Rheum.* 50(12), 3985–3993 (2004).

46 Launay D, Diot E, Pasquier E *et al*. Bosentan for treatment of active digital ulcers in patients with systemic sclerosis. *Presse Med.* 35(4 Pt 1), 587–592 (2006).

47 Denton CP, Furst DE, Matucci-Cerinic M *et al*. Bosentan prevents occurrence but does not speed healing of digital ulcers in patients with systemic sclerosis (SSc). *Rheumatology (Oxford)* 45(Suppl. 1), I154 (2006).

48 Dutz J. Treatment options for the cutaneous manifestations of systemic sclerosis. *Skin Therapy Lett.* 6(1), 3–5 (2000).

49 Robertson LP, Marshall RW, Hickling P. Treatment of cutaneous calcinosis in limited systemic sclerosis with minocycline. *Ann Rheum Dis.* 62(3), 267–269 (2003).

50 Kreuter A, Breuckmann F, Uhle A *et al*. Low-dose UVA1 phototherapy in systemic sclerosis: effects on acrosclerosis. *J. Am. Acad. Dermatol.* 50(5), 740–747 (2004).

51 Yamamoto T, Takagawa S, Katayama I, Nishioka K. Anti-sclerotic effect of transforming growth factor-β antibody in a mouse model of bleomycin-induced scleroderma. *Clin. Immunol.* 92(1), 6–13 (1999).

52 Knobler RM, French LE, Kim Y *et al*. A randomized, double-blind, placebo-controlled trial of photopheresis in systemic sclerosis. *J. Am. Acad. Dermatol.* 54(5), 793–799 (2006).

53 Romano C, Rubegni P, De Aloe G *et al*. Extracorporeal photochemotherapy in the treatment of eosinophilic fasciitis. *J. Eur. Acad. Dermatol. Venereol.* 17(1), 10–13 (2003).

54 Van den Hoogen FH, Boerbooms AM, Swaak AJ, Rasker JJ, van Lier HJ, van de Putte LB. Comparison of methotrexate with placebo in the treatment of systemic sclerosis: a 24 week randomized double-blind trial, followed by a 24 week observational trial. *Br. J. Rheumatol.* 35(4), 364–372 (1996).

55 Pope JE, Bellamy N, Seibold JR *et al*. A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. *Arthritis Rheum.* 44(6), 1351–1358 (2001).

56 Van Laar JM, McSweeney PA. High-dose immunosuppressive therapy and autologous progenitor cell transplantation for systemic sclerosis. *Best Pract. Res. Clin. Haematol.* 17(2), 233–245 (2004).

57 Farge D, Passweg J, van Laar JM *et al*. Autologous stem cell transplantation in the treatment of systemic sclerosis: report from the EBMT/EULAR Registry. *Ann. Rheum. Dis.* 63(8), 974–981 (2004).

58 Nash RA, McSweeney PA, Nelson JL *et al*. Allogeneic marrow transplantation in patients with severe systemic sclerosis: resolution of dermal fibrosis. *Arthritis Rheum.* 54(6), 1982–1986 (2006).

59 Van Laar JM, Farge D, Tyndall A. Autologous Stem cell Transplantation International Scleroderma (ASTIS) trial: hope on the horizon for patients with severe systemic sclerosis. *Ann. Rheum. Dis.* 64(10), 1515 (2005).

Affiliations

- *Audrey W Tan, MRCP*
  Clinical fellow, Department of Dermatology and Skin Sciences, University of British Columbia, Vancouver BC, Canada;
  Consultant, National Skin Centre, 1 Mandalay Road, Singapore, 308205
  Tel.: +65 6253 4455
  Fax: +65 6253 3225
  audreytan@nsc.gov.sg
- *Jan P Dutz, MD, FRCPC*
  (Dermatology, Rheumatology)
  Associate Professor, Department of Dermatology and Skin Sciences, Child and Family Research Institute, University of British Columbia, Vancouver BC, Canada
  Tel.: +1 604 875 4747
  Fax: +1 604 873 9919
  dutz@interchange.ubc.ca