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Future Options for Scleroderma Therapy

Challenges in Scleroderma Therapy

Need for biomarkers

Scleroderma is a multisystem, autoimmune, rheumatic disorder with coexisting pathologic processes such as immune system dysregulation and fibroproliferative alterations of the microvasculature (Castro and Jimenez, 2010; Hummers, 2010).

The disease is also known for its wide heterogeneity in phenotype and outcome. Owing to the complexity of the disorder and limited knowledge of its etiology, identifying patients at a risk of developing adverse outcomes and determining patient response to current therapies remain a major challenge (Hummers, 2010).

The most recent, innovative, and unbiased approaches to biomarker identification are microarray and gene expression analysis, and proteomics. Anti-Scl-70, anti-RNA pol I and III, and anti-nucleolar autoantibodies have already shown some clinical utility as aids for distinguishing diffuse systemic sclerosis (dcSSc) from limited cutaneous systemic sclerosis (lcSSc). Additionally, certain serum and plasma proteins are elevated in SSc, including biomarkers such as von Willebrand factor, adhesion molecules as well as vascular endothelial growth factors associated with vascular injury or activation such as endothelin-1, N-terminal pro-brain natriuretic peptide associated with pulmonary arterial hypertension (PAH) (Pendergrass et al., 2010), KL-6, pulmonary surfactants A and D, and pulmonary and activation regulated chemokine (PARC) associated with pulmonary fibrosis (Castro and Jimenez, 2010).

The recent establishment of an online database by the European League Against Rheumatism Scleroderma Trials and Research Group (EUSTAR), which includes clinical data of 8200 patients and recommendations for standardizing the collection, storage, and distribution of SSc biospecimens, may facilitate biomolecular studies for the development of novel biomarkers targeting therapy (Beyer et al., 2011). Moreover, similar efforts in the United States supported by a National Institutes of Health/National Institute of Arthritis, Musculoskeletal and Skin Disease Award to create National Core Centers (including Proteomic and Microarray Core Laboratories) will provide a platform for rapid advances in identification and validation of new biomarkers. The availability of well-validated biomarkers for SSc could potentially revolutionize both patient care and the identification of new therapeutics. This is particularly important because of the variability of disease progression in patients with SSc and the difficulty in predicting who will develop specific disease complications. Better biomarkers could potentially circumvent these currently vexing difficulties facing treating physicians. Biomarkers might also provide better ways to measure the extent of disease, a key part of assessing patients’ response to medications in clinical or clinical trial settings.

Several recent observations have provided new hope for biomarker development in each of these areas, particularly in relation to skin disease. Analysis of gene expression in the skin of SSc patients has shown that the degree of skin involvement in patients can be effectively measured by the degree of increased expression of 4 genes that are known targets of the cytokines transforming growth factor-beta (TGF-β) and interferon (IFN) (Farina et al., 2010). In addition, examining global gene expression in the skin of SSc patients has indicated that patients may be stratified into several different subgroups, possibly responding differently to medications (Milano et al., 2008).

Newer diagnostic tools

Apart from biomarkers, the future of effective treatment of scleroderma revolves around newer evolved tools for early diagnosis and effective prognostic evaluation. The modified Rodnan skin score (MRSS), which uses subjective,
semi-quantitative skin scoring, is the most established method for skin assessment in scleroderma patients. A new method that assesses skin health by producing and analyzing surface waves in the skin to determine its viscoelastic properties might prove to be a promising tool in the future (Zhang et al., 2011b).

Pulmonary arterial hypertension associated with SSc (PAH-SSc) has been found to have a poorer prognosis than the other forms of PAH (Campo et al., 2010). It has been shown that early therapeutic intervention, at World Health Organization (WHO) Functional Class (FC) II, can significantly improve patient survival (Galie et al., 2008). Evaluation of ventricular mass index (VMI) by magnetic resonance imaging (MRI), which correlates well with the mean pulmonary artery pressure, may play a role in predicting the presence or absence of PAH in patients in whom echocardiographic screening has failed to provide the correct diagnosis (Hagger et al., 2009). High-resolution computed tomography (HRCT) indices of alveolitis and fibrosis may be a new tool for evaluating the relationship between pulmonary involvement and systemic impairment in SSc (Bellia et al., 2009), although this technique has been validated in only a small number of SSc patients till date. Moreover, esophageal dilations visible on an HRCT scan of the chest can aid early diagnosis and specific treatment.

Microvascular damage represents the earliest morphological and functional marker of SSc and is clinically mirrored by Raynaud phenomenon (RP). Nailfold videocapillaroscopy (NVC) enables the early differentiation between primary and secondary RP by imaging and identifying morphological patterns specific to various stages of SSc; NVC patterns could increase the sensitivity of the classification criteria for SSc (Cutolo et al., 2010).

Newer diagnostic evaluators are being used for not only SSc but also localized scleroderma (LS). The Localized Scleroderma Cutaneous Assessment Tool is a promising skin scoring tool that can differentiate between activity and damage, is sensitive to change, and requires no additional equipment (Fett and Werth, 2011). Multiphoton laser scanning microscopy (MPLSM) can be used for discriminating between sclerodermatous skin and normal skin and can be used for the in vivo diagnosis and monitoring of LS (Lu et al., 2009).

**Efficacy of available treatment options**

None of the available treatment options for scleroderma have proven efficacy in preventing progression of disease, reversing fibrosis, and/or improving long-term outcome (Quillinan and Denton, 2009). A comparative analysis of the latest treatment recommendations by EULAR, EUSTAR, the German Network for Systemic Sclerosis, the European Respiratory Society, and the International Society of Heart and Lung Transplantation concluded that there is a need to clarify the definitive role of a number of new immunosuppressants and the effects of autologous stem cell transplantation in SSc because response to immunosuppressant therapy has been found to be usually weaker in SSc than in other connective tissue disorders (Opitz et al., 2011). Opitz et al. also indicated that treatment of PAH associated with connective tissue disorders follows the same algorithm as that for idiopathic PAH; however, clinical differences in therapeutic response and outcome are known to exist between PAH-SSc and idiopathic PAH groups (Benza et al., 2010; Condiliffe et al., 2009; Mathai and Hassoun, 2009; Zhang et al., 2011a). Owing to inadequate data to back clinical usage, it is not surprising that many of the treatment options used for scleroderma have been found to have limited efficacy in clinical trials. For instance, bosentan, an endothelin receptor antagonist, was recently tested in a randomized clinical trial (RCT) for the treatment of interstitial lung disease (ILD) secondary to SSc without regard to the presence of PAH. However, the authors did not find any improvement in exercise capacity between the 2 groups, thus concluding that there was no data to support the use of endothelin receptor antagonists as therapy for ILD secondary to SSc (Seibold et al., 2010). Moreover, although a number of drugs have been tested in RCTs so far, cyclophosphamide is the only drug that has demonstrated a significantly favorable effect on skin thickening associated with SSc (Tashkin et al., 2006); this shows that the available drug pool for the treatment of skin fibrosis has limited effectiveness.

**Side effects of available treatment options**

It has been observed that the side effects associated with scleroderma therapies often outweigh their effectiveness. For example, UVA-1 phototherapy showed positive short- and long-term efficacy in patients with LS, with a reduction in sclerotic plaques, an increase in skin elasticity, and a reduction in lesional skin thickness (Andres et al., 2010). However, UVA-1 therapy is also linked to short-term side effects such as erythema, pruritus, xerosis cutis, tanning, and recrudescence of herpes simplex infection (Kroft et al., 2008). Similarly, high-dose corticosteroids have side effects that may lead to renal crisis. Hence, they need to be avoided in patients with diffuse SSc, and the dosage should not exceed 15 mg/day (Busson et al., 2011; Opitz et al., 2011). According to EULAR expert opinion, “low dose of steroids are commonly used for the treatment of inflammatory arthritis in patients with SSc, but its efficacy is not substantiated by RCT” (Kowal-Bielecka et al., 2009). Although cyclophosphamide is the most commonly used therapy for SSc-associated ILD, the potential for side effects means that ideally it might be reserved for patients with progressive disease or disease refractory to other treatment (Yoo, 2010). Patients receiving disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and D-penicillamine also have occasional serious side effects, leading to their discontinuation from treatment regimen (Derk et al., 2008; Kroft et al., 2009). High-dose immunosuppressive therapy with autologous hematopoietic cell transplantation, currently under investigation in both Europe and the US, may provide the greatest hope for patients with severe progressive scleroderma and its complications. Although found to be associated with high mortality in early studies, more recent experience suggests that most patients can be treated safely with this therapy (Nash et al., 2007).
Novel Concepts and Target Sites

Drugs affecting signaling pathways

The major profibrotic signaling pathways in SSc are initiated by TGF-β, platelet-derived growth factor (PDGF), endothelin-1 (ET-1), and connective tissue growth factor (CCN2/CTGF), which function through myofibroblast differentiation and pericyte recruitment in lesional SSc fibroblasts (Leask, 2010). The signaling cascades of the cytokines TGF-β and PDGF utilize tyrosine kinases, and recent studies suggested that tyrosine kinase inhibitors like imatinib, dasatinib, and nilotinib lead to decreased production of extracellular matrix proteins (Distler and Distler, 2010; Gordon and Spiera, 2010). However, an assessment of the safety, tolerability, and effectiveness of imatinib in the treatment of PAH in a randomized, double-blind, placebo-controlled study showed that there was no significant change in 6-min walk distance (6MWD) between the 2 groups. In addition, serious adverse events occurred in 11 imatinib recipients (39%) compared to 7 placebo recipients (23%). Therefore, the effectiveness of imatinib in the treatment of PAH is questionable (Ghofrani et al., 2010). Currently, an open label study of a monoclonal antibody blocking TGF-β (GC1008/fresolimumab) is underway, possibly leading to further development of this currently unapproved drug for scleroderma and its complications. CCN2 may be another important target, as a key downstream mediator of TGF-β.

In a recent study, loss of CCN2 resulted in resistance to bleomycin-induced skin fibrosis in mice, indicating that drugs blocking CCN2 in vivo might add to the treatment armamentarium of scleroderma (Liu et al., 2011).

Another signaling molecule implicated in scleroderma is Rho-associated kinase (Rock), which is the major cellular mediator of Rho GTPase and plays an important role in the organization of actin cytoskeleton. Rock inhibition is known to benefit vascular disease and a Rock inhibitor, fasudil, is presently being investigated in a clinical trial to test its efficacy and safety in the treatment of RP (ClinicalTrials.gov identifier: NCT00498615). Rock has also been found to stimulate the differentiation of resting fibroblasts into myofibroblasts; hence, Rock inhibitors might prove to be effective drugs for SSC-associated fibrosis (Akhemtshina et al., 2008).

In comparison to healthy skin fibroblasts, dermal fibroblasts cultured from lesional areas of SSc patients have been shown to possess greater activity levels of Rac, another Rho GTPase. NSc23766, a Rac inhibitor, was shown to suppress the persistent fibrotic phenotype of lesional SSc fibroblasts (Liu et al., 2008; Xu et al., 2009). NSc23766 also blocked the elevated levels of Akt phosphorylation in SSc fibroblasts. Akt is a serine/threonine kinase that has been recently implicated in collagen regulation (Bujor et al., 2008). It has also been shown that inhibition of Akt upregulates basal matrix metalloproteinase 1 (MMP1) production and reverses the inhibitory effect of TGF-β on MMP1 gene expression; hence, Akt might be a potential therapeutic target.

The expression and function of peroxisome proliferator-activated receptor-gamma (Ppar-γ), a nuclear orphan receptor that may have a role in TGF-β-dependent fibrogenesis, have been found to be impaired in SSc. Therefore, Ppar-γ agonists could potentially be used as therapy (Wei et al., 2010; Wu et al., 2009).

A pivotal role of the ADAM-17/Notch pathway in SSc following activation by reactive oxygen species has been elucidated, indicating that this pathway may represent a new treatment target for SSc (Kavian et al., 2010) as well.

Gene targets

Investigations to understand the gene regulation cascade in the pathogenesis of SSc revealed that in response to TGF-β, the friend leukemia integration-1 (Fl1) gene is repressed through a series of post-translational modifications in which the tyrosine kinase c-Abl acts as an upstream regulator of the profibrotic protein kinase C-δ (PKC-δ)/phosphorylated-Fl1 (P Fl1) pathway. Therefore, blocking the TGF-β/c-Abl/PKC-δ/P-Fl1 pathway could be an attractive alternative approach for scleroderma therapy (Bujor et al., 2011). Rottlerin, a PKC-δ inhibitor, may also be effective as a therapeutic option (Li and Jimenez, 2011). Apart from Fl1, Egr-1 is another transcription factor that has been shown to play an important role in physiologic and pathological connective tissue remodeling (Bhattacharyya et al., 2011). Egr-1-null mice are protected from fibrosis, and Egr-1 appears to be a promising putative target for the development of anti-fibrotic therapy.

Immune modulators

Immune modulators such as belimumab (approved by the US Food and Drug Administration [FDA] for systemic lupus erythematosus), which is a monoclonal antibody targeting the B-lymphocyte stimulator protein BLYS; abatacept, which inhibits the costimulation of T cells (In clinical trial, ClinicalTrials.gov identifier: NCT00442611); and peptide human TGF-β 1 type III receptor (p144) blocker (In clinical trial, ClinicalTrials.gov identifier: NCT00574613) are currently under investigation in clinical trials for alleviation of skin fibrosis.

Miscellaneous drugs/drug targets

A few other drug targets and potential therapy options include the following: oral collagen I for relieving skin fibrosis (In clinical trial. ClinicalTrials.gov identifier: NCT0005675); caveolin-1 which at reduced levels in lung fibroblasts promote collagen overexpression and lung fibrosis through stimulation of TGF-β signaling (Del Galdo et al., 2008a; Del Galdo et al., 2008b; Tourkina et al., 2010); tumor necrosis factor-related weak inducer of apoptosis (TWEAK) which when elevated could be a protective factor against the development of pulmonary fibrosis (Yanaba et al., 2009); serum amyloid P (SAP) which has been shown to reduce bleomycin-induced pulmonary fibrosis in rats (Pilling et al., 2007); taurine, an antioxidant which inhibits the production of proinflammatory cytokines such as interleukin (IL)-1 and IL-6 along with the production of TGF-β (a major fibrogenic cytokine involved in scleroderma) (Fallahzadeh et al., 2010); microRNA-29 which when down regulated in SSc fibroblasts increased the levels of profibrotic genes (Maurer et al., 2010); synthetic cannabinoid receptor agonist WIN55,212-2, which prevented skin fibrosis in a bleomycin-induced mouse model of scleroderma (Balisteri et al., 2011); and retinoic acid, which can modulate connective tissue metabolism and exhibit anti-fibrotic activity, thereby improving the clinical symptoms of SSc (Xiao et al., 2011).

N-acetylcysteine can ameliorate vascular renal function in patients with low disease severity (Rosato et al., 2009).
A proliferation-inducing ligand (APRIL, a member of the tumor necrosis factor family), which plays an important role in the survival of peripheral B cells, may contribute to the pathogenesis of SSc through the upregulation of autoantibody production and maintenance of autoimmune phenomena (Bielecki et al., 2010).

**Monotherapy versus combination therapy**

Despite absence of firm evidence from RCTs, combination therapies are often used for patients deteriorating on monotherapy (Keogh et al., 2011). Since a number of cellular pathways are implicated in SSc, many clinicians consider that simultaneous blockade of these pathways might produce better and longer-lasting results (Ramos-Casals et al., 2010). A recent (January 2005 to August 2009) Australian collaborative report on 112 patients with WHO-FC II-IV PAH who were deteriorating on monotherapy and therefore received a non-parenteral combination therapy, which included bosentan, or sitaxsentan, or ambrisentan, or iloprost, or sildenafil, showed that survival with dual therapy in patients with idiopathic PAH/familial PAH was 93% at 1 year and 79% at 2 years, and in patients with PAH-SSc, survival was 72% at 1 year and 48% at 2 years. In survivors, dual therapy reversed deterioration in FC, from 3.1 ± 0.6 on monotherapy to 2.2 ± 0.6 at 12 months. Similarly, dual therapy improved 6MWD, and sequential echocardiography demonstrated a fall in pulmonary artery systolic pressure and improved right ventricular function (Keogh et al., 2011). Commonly used dual therapy include prostaestacynl analogs plus endothelin antagonists or phosphodiesterase inhibitors (McLaughlin et al., 2010; McLaughlin et al., 2006; Simonneau et al., 2008).

**Comorbid hyperlipidemia**

Mild dyslipidemia and a high atherogenic ratio (LDL-C/HDL-C) found in SSc patients has led to hyperlipidemia being a risk factor for hemodynamic disturbances in these patients (Kozlova et al., 2001; Tsifetaki et al., 2010). Therefore, lipid profiling (especially measurement of lipoprotein[α]) in scleroderma patients has been suggested (Lippi et al., 2006). HMG-CoA reductase inhibitors (or statins), which lower cholesterol levels, were found to aid in treating RP and digital ulcers in SSc patients by retarding vascular injury (Abou-Raya et al., 2008). The lysophospholipids lysophosphatidic acid and sphingosine 1-phosphate levels are elevated in the sera of SSc patients and may be targeted in SSc therapy (Pattanaik and Postlethwaite, 2010; Tokumura et al., 2009).

**Conclusion**

The plethora of drug targets and treatment options being tested for scleroderma raise hope for more effective, targeted therapies to emerge in the near future. Furthermore, as most of the molecular targets for drug development are still being tested in cell lines and bleomycin-induced mouse models, there is an urgent need to translate the results obtained at the bench to the clinic. There is also a need to discover newer drugs for known target sites and also newer disease-specific target sites for efficacious drug development with minimal side effects.

**References**


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Due to increasing interest and an ever-widening field of inquiry in scleroderma research, the Scleroderma Foundation has created a Medical Professionals Membership Program.

“It was not many years ago that scleroderma research was being done by a relatively small group of investigators,” said Dr. John Varga, the Chair of the Scleroderma Foundation Medical Advisory Board. “Today, however, we see advances in scleroderma and diseases related to it spreading over an increasingly wide area. Along with progress comes change. It is more difficult to stay in touch with studies and research than ever before.”

The program is meant to help researchers and clinicians by providing a one-stop shop where they can learn the latest about what is happening with scleroderma treatment and research in addition to having access to a wide variety of resources.

The program is helpful to medical professionals who specialize in several fields that overlap with the symptoms of scleroderma. These fields include rheumatology, dermatology, gastroenterology, pulmonologists, pediatricians, and family practitioners.

Members receive articles, pamphlets and Scleroderma Information Packets at no charge; a complete listing on the Medical Member section of the Foundation’s high visibility Web site; discounts for the national patient conference and special events; periodic eLetter updates about new or advancing research; and five copies of our quarterly magazine, the Scleroderma Voice.