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The Current State of Biomarkers in Systemic Sclerosis

Laura K. Hummers

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Abstract Scleroderma is a complex, multisystem autoimmune rheumatic disease with wide heterogeneity in phenotype and outcome. There are often coexisting ongoing pathologic processes including immune system activation, progressive fibrosis, and vascular disease in subsets of patients. Currently, it is challenging to identify patients at risk for developing adverse outcomes and to determine which patients are responding to current therapies. For these reasons, it is highly valuable to find easily measurable biomarkers that may represent ongoing disease activity or treatment response. This review examines the current state of biomarker development in systemic sclerosis and identifies areas in which further work should be directed.

Keywords Scleroderma · Biomarkers · Fibrosis · Pulmonary hypertension

Introduction

When confronted with a newly diagnosed patient with systemic sclerosis, clinicians must determine who may develop early progressive fibrosis and who is at risk for future pulmonary arterial hypertension (PAH). The early clinical features of the disease may provide some guidance. A patient with edematous skin, new development of Raynaud phenomenon, and antibodies to topoisomerase-I has a higher likelihood of having more skin and lung fibrosis early in the disease course. This may be helpful in initial risk stratification, but even this type of fine-tuned phenotyping is not specific enough to be the sole basis of treatment decisions. In those patients who we elect to treat, our current response measures are not particularly sensitive to change in the interval that is most clinically relevant. Determining which patients will develop the progressive vasculopathy that characterizes PAH and ischemic digital ulcerations, or the more abrupt vascular insult of renal crisis, is also fundamentally important. Autoantibody specificity may offer some value in specific situations (RNA polymerase I/III in determining risk of renal crisis), but lacks sufficient sensitivity and specificity (roughly half of renal crisis patients do not produce this antibody and only 30% to 40% of antibody-positive patients develop renal crisis) [1]. The ability to better risk stratify patients is one of the key potential uses of biomarkers. An ideal biomarker measures pathways fundamental to disease pathogenesis, predicts future development of relevant outcomes, is easily measurable, and changes with effective therapy. At present, no measures fulfill these criteria, but areas exist in which progress has been made. In addition, multiple novel therapies are being investigated that may provide an ideal setting for investigating potential markers.

The list of possible uses of biomarkers in scleroderma is long. The disease is difficult to objectively measure and aspects of the disease may change slowly with time or may smolder. Several areas, however, likely have the most urgency and the highest likelihood for discovery of a tenable biomarker. These areas include assessment of activity in the skin or lung in patients with early disease, and determination of the risk for development of clinically significant vascular events (PAH, digital ulcers, renal crisis) and intermediate end points for clinical trials

L. K. Hummers (✉)
Division of Rheumatology, Johns Hopkins Scleroderma Center,
Johns Hopkins University,
5501 Hopkins Bayview Circle, Room 1B.7,
Baltimore, MD 21224, USA
e-mail: lhummers@jhmi.edu

that examine mechanisms of the drug or relevant biologic pathways.

Assessing Disease Activity and Risk for Progressive Skin and Lung Disease

The earliest features of scleroderma are inflammatory in nature. Early scleroderma skin disease is edematous, with histopathologic analysis revealing dermal inflammation and patients with lung involvement demonstrating a mixed inflammatory infiltrate by cytopathology. This process is thought to precede activation of fibroblasts, which may then sustain fibrosis independently. Therefore, multiple cellular pathways may be exploited to yield a measurable marker. In terms of clinical measurements that may assess activity, there are nonspecific markers of inflammation such as erythrocyte sedimentation rate and C-reactive protein (CRP). Some of these nonspecific markers have been incorporated into disease activity measures (eg, Valentini disease activity index) that have some validity [2]. These nonspecific markers have not been shown to predict outcome and are independent of any direct measurement of mechanism, but they could be modifiable by therapy.

Profibrotic cytokines, such as transforming growth factor β (TGF-β) and connective tissue growth factor (CTGF), are clearly abnormal in scleroderma and involve abnormal tissue expression, implicating them in disease progression. As such, they may be relevant therapeutic targets. CTGF levels (or its cleavage products) have consistently been found to be elevated in the peripheral blood in scleroderma, correlate with skin and lung fibrosis, and are higher in earlier disease, implicating a role in the development or early progression of the fibrotic phenotype [3, 4]. In other fibrosing diseases (eg, diabetic nephropathy), CTGF levels may be predictive of outcome, but longitudinal studies in scleroderma have not been performed. TGF-β levels have inconsistently been found to be abnormal in scleroderma serum, potentially reflecting either measurements of different disease phase or perhaps more likely that there is sequestration of the molecule in affected sites [5]. An interesting new avenue of investigation is the measurement of TGF-β-responsive gene signature in the skin biopsies of scleroderma patients [6••]. These data also suggest that this signature is expressed more strongly in patients with more extensive skin and lung disease. This type of approach may lead to further mechanistic approaches to therapy and may possibly be usable as intermediate biologic end points in early-phase clinical trials [7].

Markers of collagen turnover have been examined in cross-sectional study and in some clinical trials [8]. The most commonly studied markers of collagen turnover include serum N-terminal pro-peptide of type I (PINP) and type III (PIIINP) collagen; C-terminal pro-peptide of type I collagen; cross-linked carboxyterminal telopeptide of type I collagen; and C-terminal telopeptide of type I collagen. Of these, PIIINP has been the most thoroughly investigated in the past 20 years. Studies have suggested elevated levels in the serum of scleroderma patients and some correlation with degree of skin involvement lung involvement and to some extent disease progression [9–12]. The use of immunosuppressant therapy has been associated with a decrease in PIIINP levels [13]. Markers of collagen synthesis have been investigated in a placebo-controlled study of the CAT-192, an anti-TGF-β monoclonal antibody. In this study, PINP correlated with changes in modified Rodnan skin score. However, levels of PIIINP did not. Another study, however, suggested that levels of PIIINP decreased in an open-label study of 16 patients treated with infliximab, but skin scores did not improve in this 26-week trial. A systematic review of available data in 12 cross-sectional studies examining serum markers of collagen turnover was performed in 2004 by Dziadzio et al. [14]. This study demonstrated wide heterogeneity in methodology, clinical data reporting, and small sample sizes [14]. The authors conclude, however, that longitudinal study should still be pursued as the limitations of the prior studies did not preclude the potential utility of these markers.

Bronchoalveolar lavage fluid measurement of neutrophilia and eosinophilia had been demonstrated in retrospective studies to correlate with a high risk of progressive decline in lung function [15], but this association did not hold when data from the Scleroderma Lung Study (SLS) were evaluated [16]. Several serum glycoproteins have been examined as potential markers of progressive lung involvement in scleroderma. They are both produced by type 2 alveolar epithelial cells. Increased levels have correlated with higher risk for interstitial lung disease (ILD) progression in scleroderma and may diminish with cyclophosphamide therapy [17]. Evaluation of samples from subjects screened or enrolled in the SLS study demonstrated the serum levels of both surfactant protein D (SP-D) and Kl-6 correlated with “alveolitis” (defined by bronchoalveolar lavage [BAL] or high-resolution CT per the SLS protocol) and extent of CT fibrosis and, to some extent, lung function parameters [18•]. This study found SP-D to be fairly sensitive (89%) and Kl-6 to be specific (90%) as markers of “alveolitis.” This study could not assess response to therapy because of the limited number of samples. More recently, several chemokines, including Chemokine (C-C motif) ligand 18 (CCL18), Chemokine (C-C motif) ligand 2 (CCL2) and chemokine (C-X-C motif) ligand 10 (CXC10) have been evaluated as markers of lung disease in scleroderma. Gene expression profiles

from BAL fluid showed increased expression of chemokines and chemokine receptor genes [19]. Serum levels of CCL18 are associated with the presence of ILD in patients with scleroderma and possibly correlated with active lung disease more closely than KL-6 and SP-D, although the number of patients in this study was small [20]. When concurrently examined in serum and in cultured cells from BAL supernatants, CCL18 was noted to be increased in those with lower lung function and BAL neutrophilia/eosinophilia, and an increase in CCL18 positive alveolar macrophages was noted by flow cytometry [21]. CCL2 was examined in a large sample of scleroderma patients and noted to be elevated in some patients with both limited and diffuse scleroderma and in the diffuse patients the elevations were associated with early disease but not with pulmonary vascular disease [22•].

Prediction of Risk and Progression of Vascular Disease

Although the development and progression of fibrotic skin and lung disease is typically a concern at disease onset, the major clinically relevant vascular events, such as the development of clinically evident pulmonary hypertension occur years into the disease. In general, less is known about clinical risk factors that predict pulmonary hypertension development. For example, the autoantibody associations are not as strong, likely reflecting the heterogeneous cascade of events that may lead to pulmonary vascular disease (hypoxia from ILD, primary pulmonary vasculopathy, direct myocardial insult), and some antibodies that associate with the phenotype are not widely commercially available [23]. Strong circumstantial evidence also exists of a long preclinical disease state; it is widely recognized that the diffusing capacity of the lung for carbon monoxide (DLCO) drops perhaps years before clinical onset of disease [24]. This is an ideal situation for the development of a biomarker that could be used for risk stratification purposes, with potential ability to speed the diagnosis, intensify screening or diagnostic algorithms, or even change disease course by instituting therapy at a less advanced state [25]. A problem, however, is that the biology of the process is extremely complex, involving perturbations of multiple cell types and biologic pathways. In addition, many of the markers have pleiotropic effects, may either reflect ongoing insult or accumulated damage, or may not be specific to the clinical phenotype of interest (ie, the relationship to pulmonary vascular disease is confounded by an association with peripheral vascular disease). These problems, however, are not insurmountable if measurements are taken from large cohorts of prospectively followed, well-characterized patients. To date, most of the investigations of biomarkers in vascular disease in scleroderma come from relatively small cross-sectional studies, with variable attention to clinical phenotype.

Clinical Markers

DLCO

Several investigations have examined the predictive capability for the DLCO for the development of clinically significant pulmonary vascular disease. It has long been recognized that diminished DLCO is a poor prognostic indicator [26, 27]. In addition, it has been noted that DLCO is severely depressed years before a patient develops clinically recognized isolated PAH [24]. In a prospective evaluation of 384 patients with complete data collection and no pulmonary hypertension at baseline, 18 patients developed pulmonary vascular disease over a median follow-up time of 41 months (8 patients with PAH, 8 patients with pulmonary venous hypertension, and 2 patients associated with severe ILD) [28]. In this study, those with incident PAH had a significantly lower DLCO than those with no PH at baseline (54% vs 73% predicted; P=0.02). In another single-center cohort study of 101 scleroderma patients, the eight patients who developed PAH during 28 months of follow-up, had a significantly lower DLCO (58% vs 80% predicted; P=0.002) and a DLCO/alveolar volume (VA) less than 70% predicted carried an HR of 18.8 (95% CI, 1.7–206.8) for development of PAH in multivariate analysis and DCLO/VA less than 60% predicted an HR of 36.7 (95% CI, 3.45–387.6) [29•]. By receiver operating characteristic analysis, the sensitivity and specificity of a DLCO/VA less than 70% predicted were 87.5% and 79.5%, respectively, and a DLCO/VA less than 60% were 62.5% and 88.1%, respectively.

Brain Natriuretic Peptide

Brian natriuretic peptide and its N-terminal prohormone are secreted by ventricular myocytes in response to stretch, hypoxia, and by certain neurohormonal stimuli. Among scleroderma patients, these hormones correlate with hemodynamic, echocardiographic, and functional measurements of pulmonary vascular disease [30]. Levels of N-terminal prohormone brain natriuretic peptide (NT-proBNP) are disproportionately higher in patients with scleroderma-associated PAH compared with idiopathic PAH and also associate with higher risk of mortality [31, 32]. It is thought to have an extremely high negative predictive value for diagnosis of PAH [32]. Allanore et al. [29•] also explored NT-proBNP in a prospective cohort of scleroderma subjects followed for incident development of PAH. This study found that NT-proBNP levels, at a threshold of more than

97% manufacturer-provided normal levels carries a significant HR for the future development of PAH, which is enhanced by measures of DLCO. Measurement of BNP may likely enhance our ability to diagnose early pulmonary vascular disease, and as such may prove to be quite a useful adjunct to current screening methodologies. It is not known, however, if levels measured at an even earlier stage that still fall within typical levels of normal may still have some predictive value, as is the case with high-sensitivity CRP and coronary artery disease. Also, because the measure is not specific to the right ventricle, this marker may have low specificity to PAH, as patients may have pulmonary venous hypertension or other cardiac dysfunction.

Endothelial Markers

Endothelial insult may be the earliest pathologic feature in scleroderma [33]. Damage to the endothelium itself or the downstream effects in the surrounding tissues may lead to a host of consequences leading to end-organ damage. Measures of endothelial cell damage, such as von Willebrand factor (vWF), in cross-sectional studies, consistently find elevated levels [34], although correlation with clinical evidence of vascular disease is not clear [35, 36]. Endothelin-1 is a potent vasoconstrictor secreted from multiple cell types including the endothelium and is overexpressed in the vessels of scleroderma tissues [37]. Elevation of endothelin-1 in the plasma of scleroderma patients is widely reported [38], but a clear association with vascular phenotypes in scleroderma is lacking. Given the suggested role of endothelin-1 in the pathogenesis of pulmonary vascular disease and potential role in inducing fibrosis, it may still be a molecule with potential as a biomarker for scleroderma possibly for vascular or even fibrotic disease [39]. However, given that levels seem to be elevated in broad populations of scleroderma patients, it may lack sufficient specificity to one process (eg, PAH) and may not be discriminating enough as a predictive tool.

Adhesion molecule expression is induced by endothelial cell damage and this, in turn, may lead to further damage by allowing the transmigration of inflammatory cells. Increases in a number of circulating adhesion molecules (soluble intercellular adhesion molecule-1 [sICAM-1]; soluble vascular adhesion molecule 1 [sVCAM-1]; E-selectin) have been seen in scleroderma patients with some association with some vascular phenotypes [40]. One small study noted that levels of VCAM-1, ICAM-1, and vWF were elevated in patients with scleroderma and PAH (and scleroderma without PAH), but levels of the adhesion molecules (not vWF) diminished to within normal range in those with PAH treated with bosentan [36].

Angiogenic Markers

There is substantial evidence for imbalanced angiogenesis as a contributing factor for scleroderma vascular disease. Plasma from scleroderma patients is associated with a decrease in endothelial tube formation in in vitro assays [41•]. Circulating factors influencing local tissue angiogenesis include growth factors and inhibitors of angiogenesis such as endostatin and angiostatin. Studies of the peripheral blood of scleroderma patients demonstrate abnormalities in angiogenic factors including growth factors (vascular endothelial growth factor [VEGF], fibroblast growth factors, placental growth factor, platelet-derived growth factor, and hepatocyte growth factor [HGF]), metallomatrix proteinases, and angiostatic molecules (endostatin, thrombospondin, angiostatin, soluble endoglin).

Despite clear clinical evidence of a diminution of new blood vessel growth in scleroderma, some potent angiogenic growth factors are consistently elevated. VEGF is the most widely studied. Although some studies suggest that elevated levels of VEGF correlate with phenotype, a correlation with vascular events is not as clear [42, 43]. It has been suggested that initially, VEGF may be of benefit in reducing damage to small blood vessels, but chronic overexpression may even be deleterious [42, 44]. This may be combined with an overproduction of angiostatic molecules including soluble VEGF receptors, endostatin, angiostatin, and soluble endoglin. Endostatin is a potent inhibitor of angiogenesis and levels are increased in the scleroderma group compared with control patients and may correlate with pulmonary and peripheral vascular disease [43, 45]. Soluble endoglin has been noted to be elevated in several studies and a more clear association with vascular phenotypes is noted [46••, 47]. The soluble VEGF receptors and soluble endoglin are of particular interest given their predictive ability in other disease states such as preeclampsia [48]. An imbalance of the regulators of angiogenesis with an increase in circulating inhibitors and a decrease in some growth factors such as HGF could lead to imbalanced vascular repair mechanisms and prevent the normal responses of ischemic injury. Although these studies all point to potential mechanisms of how defects in angiogenesis may play a role in the marked vascular abnormalities seen in scleroderma, none of these factors have been evaluated in a group of patients prospectively to assess their potential as predictors of outcome in severe vascular events.

Prediction of Response to Therapy

There are two important aspects of biomarkers that are assessed as part of a clinical trial. There are markers that

assess if the agent being studied has had its intended biological effect and markers that may be used as intermediate end points for a desired clinical outcome. Ideally, one marker would fulfill both roles. Clinical trials are an ideal setting for examining potential biomarkers. A typical clinical trial in scleroderma selects groups of patients that are relatively homogeneous, manifest a particular component of scleroderma (early active skin, active lung, digital ulcerations) and have longitudinal follow-up and sample collection. It is vital that biomarker development be included in the planning of all future clinical trials in scleroderma and that data and samples from completed clinical trials be used for this purpose.

Conclusions

The development and validation of biomarkers in scleroderma may help to improve the risk stratification of patients at onset, target screening to higher risk subsets, select patients who may have improved response to therapy, determine who is responding to therapy at an earlier stage, and potentially lead to new therapeutic targets. Assessments of biomarkers must occur in large cohorts of patients with specific attention to fine clinical phenotyping and ideally with longitudinal data focusing on selected outcomes. Attention in biomarker development should focus on their discriminatory value for specific clinical features and outcomes within scleroderma, rather than searching for those markers that are uniformly and strikingly different compared with control populations. In addition, it is vital that biomarker development strategies be incorporated into the development planning for all clinical trials.

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