Biomarkers of vascular disease in scleroderma

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Vascular disease is present in every patient with scleroderma and is a major source of morbidity and mortality. There is a subset of patients who will develop severe and sometimes life-threatening vascular events. We have good evidence that an insult to the microvasculature occurs early in the disease course, but there is a subset of patients who have an ongoing chronic process, the end result of which are events such as digital loss and pulmonary arterial hypertension. The ability to detect this process at an early stage by simple means would be of great value as our ability to treat these vascular complications improves with time. We have a significant amount of evidence of vascular perturbation from studies of peripheral blood in scleroderma, but know very little about the ability of these biomarkers to predict vascular outcomes. In this review, we will critically assess our current knowledge of the use of biomarkers of vascular disease in scleroderma and the possible directions of future research in this area.

The potential utility of biomarkers in scleroderma vascular disease

The term biomarker is commonly found in the medical literature but is often misused. The NIH Biomarkers Definitions Working Group defines a biomarker as ‘A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention’ [1]. An ideal biomarker reflects the underlying biologic process, predicts clinical events in the absence of treatment and is easily obtainable. This typically requires validation in a longitudinal cohort study. For the study of scleroderma vascular disease, biomarkers may serve three important roles:

- Help understand pathological mechanisms.
- Predict the development of vascular complications (i.e. pulmonary hypertension) in a susceptible population.
- Define response to therapy.

Selected data from biomarker studies in scleroderma

An exhaustive review of all of the data on potential biomarkers of scleroderma vascular disease is beyond the scope of this article. We highlight here some examples of the potential of certain biomarkers to serve as surrogates for the vascular disease process in patients with scleroderma.

Biomarkers to investigate pathogenesis

Numerous cross-sectional studies have investigated markers of possible pathogenic processes of scleroderma vascular disease. Typically, these studies have shown clear evidence of perturbation of the vascular bed suggesting possible endothelial cell dysfunction, abnormalities of vascular smooth muscle, altered fibrinolysis and coagulation or angiogenic imbalance. Almost all of these studies have examined a cross-section of unselected scleroderma patients, measuring the possible biomarkers at one point in time. A smaller number of studies have correlated these measures with clinical data (e.g. the presence of diagnosed vascular disease such as pulmonary hypertension) or have measured factors longitudinally. For example, Hesselstrand et al. [2] examined several circulating markers [von Willebrand factor as a marker of endothelial perturbation, thrombomodulin as a marker of vascular injury, pro-brain natriuretic peptide (BNP) as a marker of right ventricular dysfunction and calcitonin gene-related peptide] in a longitudinal study of patients with and without echocardiographic evidence of pulmonary hypertension. Only pro-BNP correlated with a tricuspid gradient in a group of scleroderma patients with serial echocardiograms. Distler et al. [3] found increased VEGF levels in scleroderma compared to controls; higher levels were found in early disease and in topoisomerase positive patients but were negatively associated with finger ulcerations. Others have suggested that VEGF levels may also be modified by therapy directed at the vascular disease [4].

Many studies have attempted to investigate pathological mechanisms of a poorly understood process. This is clearly a worthwhile endeavour. However, there are multiple limitations to this approach (Fig. 1). The biological effects of many markers (such as VEGF) are pleiotropic and may vary over time and vary with different stages of disease. Many of these studies have been limited by lack of good control populations; therefore, the specificity of the marker to the scleroderma disease process is unknown. It is unclear if these markers are measuring ongoing vascular events or terminal damage to the vascular bed. Despite these limitations, we are likely to learn some incremental information about the vascular disease process with the accumulation of data from these investigations. Validation of these biomarkers, however, will require longitudinal, well-controlled, prospective studies.

Biomarkers as a predictor of development of pulmonary hypertension

Biomarkers that predict specific clinical events (such as development of pulmonary hypertension) have yet to be identified. Multiple studies have demonstrated circumstantial evidence of an ongoing vascular insult that predates the clinical diagnosis of pulmonary hypertension. Steen et al. [5] reported a marked decrease in the diffusing capacity for carbon monoxide (DLCO) years prior to the diagnosis of pulmonary hypertension in a retrospective case-control study. The increasing interest in the scleroderma vascular disease and the presence of multiple scleroderma-specific centres around the world will allow for prospective evaluations of potential predictors of adverse outcomes including pulmonary hypertension. A recent study by Allanore et al. [6] investigated the levels of N-terminal pro-BNP (NT-pro-BNP) and low DLCO as biomarkers to predict the development of pulmonary arterial hypertension (PAH). This study followed a prospective cohort of 101 patients without PAH.
Vascular disease is a fundamental part of scleroderma pathogenesis and is characterized by marked heterogeneity of expression, long periods of preclinical activity and in a subset of patients is the major source of morbidity and mortality. Circulating factors that reflect ongoing vascular perturbation have the potential of serving as intermediate biological endpoints that can not only detect and characterize vascular disease activity but also predict ultimate disease outcome or treatment response. In order to realize fully the benefit of biomarkers, several factors must be incorporated into study design. For studies examining pathogenic mechanisms, appropriate control groups and longitudinal assessments are necessary to ensure specificity and reliability. If a marker is investigating predictive ability for vascular outcomes, prospective cohorts with well-characterized patients and well-defined outcomes are necessary. Potential biomarkers should be incorporated into clinical trials, although confounding factors will have to be taken into account. Our ability to understand and to manage scleroderma vascular disease will explode in the upcoming years, making this the ideal time to investigate the great potential of biomarkers in this field.

**Biomarkers as surrogate endpoints in clinical trials**

Fortunately, several classes of medications are now approved for the treatment of PAH with data from well-designed clinical trials that have all included patients with scleroderma. The primary and secondary outcomes of these trials include functional capacity (6-min walk testing, WHO classification), clinical worsening (including change in therapy, hospitalization, need for lung transplant) and physiological parameters (cardiac index). All of these outcomes have some limitations and this is an area where the use of biomarkers as a surrogate endpoint may be of great value in predicting ‘harder’ outcomes such as death or clinical worsening (for a complete review on this topic, refer to [7]). Unfortunately, published clinical trials have not included investigations of possible surrogate markers. ET-1 seems like a logical choice, particularly since levels are elevated and correlate with the severity of PAH. However, since dual ET receptor antagonists are likely to increase circulating levels of ET and due to the very short half-life of the molecule in circulation, this may not be a good candidate for all clinical trials [8]. Sfikakis et al. [9] studied markers of endothelial function in scleroderma patients treated with bosentan for either pulmonary hypertension or digital ulcerations. They found no difference in the levels of ICAM-1, E-selectin, VEGF or ET-1 after 4 and 16 weeks of treatment with bosentan.

Multiple studies have investigated BNP and NT-pro-BNP. These markers are increased in patients with PAH, which are linked to pleotropic effects of many circulating factors including mortality [10]. Adjunctive therapies (diuretics, etc.) may decrease during therapy and correlate with improving hemodynamic parameters [10]. Screening for pulmonary hypertension in systemic sclerosis: the longitudinal development of tricuspid gradient in 227 consecutive patients, 1992–2001. Rheumatology 2005;44:366–71.

**References**

3 Distler O, Del Rosso A, Giacomelli R et al. Angiogenic and angiostatic factors in systemic sclerosis: increased levels of vascular endothelial growth factor are a feature of the earliest disease stages and are associated with the absence of fingertip ulcers. Arthritis Res 2002:4;R11.