Heart Involvement in Patients with Systemic Sclerosis Is Mimicked by Fra-2 Transgenic Mice

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Pathogenesis of systemic sclerosis (SSc)

- Vascular damage
- Inflammation and autoimmunity
- Excessive collagen production and deposition

Disclosures

- O. Distler has consultancy relationships and/or has received research funding from Actelion, Pfizer, Ergonex, BMS, Sanofi-Aventis, United BioSource Corporation, medac, Biovitrium, Novartis, 4D Science and Active Biotec in the area of potential treatments of scleroderma and its complications

- J. H.W. Distler has consultancy relationships and/or has received research funding from Actelion, Pfizer, Ergonex, BMS, Celgene, Bayer Pharma, JB Therapeutics, Sanofi-Aventis, Novartis, Array Biopharma and Active Biotec in the area of potential treatments of scleroderma and its complications and also is stock owner of 4D Science.

Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database

- Of the SSc-related deaths 26% to cardiac causes

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Primary causes of death in 234 patients with SSc</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>All deaths cases</td>
<td>234</td>
</tr>
<tr>
<td>SSc-related death cases</td>
<td>128</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>78</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>45</td>
</tr>
<tr>
<td>Isolated PAH</td>
<td>33</td>
</tr>
<tr>
<td>Myocardial</td>
<td>33</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>14</td>
</tr>
<tr>
<td>Left heart failure</td>
<td>8</td>
</tr>
<tr>
<td>Right heart failure</td>
<td>5</td>
</tr>
<tr>
<td>Biventricular heart failure</td>
<td>4</td>
</tr>
<tr>
<td>Pericardial (constrictive and/or tamponade)</td>
<td>2</td>
</tr>
<tr>
<td>Renal</td>
<td>10</td>
</tr>
<tr>
<td>Renal crisis</td>
<td>5</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>10</td>
</tr>
</tbody>
</table>

Ann Rheum Dis 2010
Microvascular Damage and Cardiac Fibrosis Detected by Heart MRI are a Hallmark of Systemic Sclerosis Heart Involvement

Abstract 2484
Tatiana Sofia Rodriguez-Reyna et all

- 62 SSc patients;
- 45% showed detectable myocardial fibrosis; myocardium affected by fibrosis was 6.7% in dcSSc and 1.6% in lcSSc.
- 79% showed perfusion defects

Background and Aim:

- SSc-related cardiomyopathy is increasingly recognized as a major cause of death.
- However, the pathogenesis of SSc-related cardiomyopathy is poorly understood.
- New therapies as well as platforms for testing are needed.

Aim – to characterize different murine models of SSc and identify the best animal model for SSc-related cardiomyopathy.

Materials (1):

- Six patients with SSc (according to LeRoy) without cardiac involvement were enrolled in the project
- Age- and sex- matched patients autopsies served as controls
- Patients with a medical record for cardiovascular disease were excluded from the study

Materials (2):

1. Fra-2 transgenic mice model (Fra-2). Fra-2 member of activating protein 1 family. Dermal and lung fibrosis. Fibrosis preceding loss of capillaries due to increased endothelial apoptosis.
2. Sclerodermatous chronic Graft vs. Host disease (GvHD) model. Sub-lethally irradiated BALB/c mice; transplanted with minor histocompatibility complex mismatched bone marrow; pulmonary and dermal fibrosis.
3. Tight skin 1 mutation model (Tsk-1). Tandem duplication in Fibrilin 1 gene in B10 mice. Dermal and hypodermal fibrosis, auto antibodies (topoisomerase I, dsDNA).
Capillary loss in SSc heart tissue

Vascular damage in heart tissue

Increased fibrosis in heart tissue

Conclusion:

- Typical features of cardiac disease in SSc – loss of capillaries due to apoptosis of endothelial cell and fibrosis - are closely mimicked by Fra-2 tg mice.

- The changes in the hearts of mice with sclerodermatous cGvHD and in Tsk-1 mice were less representative.

- Fra-2 tg mice are a promising preclinical model to study the mechanisms and therapeutic approaches of heart involvement in systemic sclerosis.
Acknowledgements

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Thank you!