Progressive Systemic Sclerosis- from the molecular background to innovative therapies

Peter Szodoray¹, Emese Kiss²

¹Immunobiological Laboratory, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway, ²National Institute of Rheumatology and Physiotherapy, Budapest, Hungary

TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Therapeutic approaches in systemic sclerosis
   3.1. Immune-modulating treatment
   3.2. Medications, affecting rheological parameters
   3.3. Anti-fibrosis agents
   3.4. Symptomatic treatment
4. Novel immune-modulating approaches
   4.1. Autologous stem-cell transplantation (ASCT) in systemic sclerosis (SSc)
   4.2. Extracorporeal photochemotherapy in systemic sclerosis (SSc)
5. Concluding remarks
6. References

1. ABSTRACT

Systemic sclerosis (SSc) is a complex autoimmune disorder. The cornerstones of the pathogenesis are vascular damage, fibrogenesis and various cellular and humoral autoimmune processes. The aim of the present review is to describe pathogenic steps, leading to the hallmark clinical picture of SSc. Indeed, numerous therapeutical approaches have been tested/are in use, directed towards vascular damage, fibrogenesis, as well as autoimmune processes in order to decelerate the progression of the disease. These therapies are also discussed in the review. Finally, we described certain novel immune-modulating possibilities, namely autologous stem-cell transplantation and extracorporeal photochemotherapy.

2. INTRODUCTION

Systemic sclerosis (SSc) is a prototypical systemic autoimmune disease, characterized by a wide spectrum of clinical manifestations, driven by disproportional collagen deposition in the blood vessels, skin and internal organs (lungs, heart, gastrointestinal tract, kidneys). Probably, the earliest pathological changes in patients with SSc are in the endothelial cell function leading to the damage of the microvasculature (1, 2). This initial damage is subsequently followed by inflammatory cell-migration, leading to a wide array of endothelial injuries, namely arterial intimal fibrosis and extensive functional loss of these blood vessels (3).

The pathology behind the uncontrolled fibrotic
Pathogenesis and therapy of SSC

Processes are partly driven by cytokines and growth factors, such as transforming growth factor-beta (TGF-β), connective tissue growth factor (CTGF), platelet-derived growth factor (PDGF), as well as and endothelin-1 (ET-1), secreted in the skin and lungs, leading to fibroblast activation, promoting accumulation of collagen, proteoglycans, fibronectin, elastin, as well as tenascin (4). Besides these factors, other cytokines e.g. interleukin (IL)-13, IL-21, chemokines, including CCL2 (monocyte chemoattractant protein-1 (MCP-1)/(MCAF) and macrophage inflammatory protein 1-beta (MIP-1β)), angiogenic factors, namely vascular endothelial growth factor (VEGF), peroxisome proliferator-activated receptors (PPARs), acute phase proteins, as serum amyloid P protein (SAP), caspases, and components of the renin-angiotensin-aldosterone system (ANG II) have been identified as important regulators of fibrosis (5), therefore may also be relevant in the development of fibrosis in SSc.

Bone marrow-derived mesenchymal progenitor cells, denoted as fibrocytes maintain a constant re-load for the expanding fibroblast population within the fibrotic lesional tissue in SSc, therefore further contribute to the connective tissue accumulation (6). The aforementioned locally produced chemoattractant factors drive this migration, leading to fibrosis and eventual organ damage. Moreover, the biosynthesis of collagen molecules involves several intracellular post-translational modifications, followed by excretion and extracellular aggregation of the collagen molecules into fibrils, which are subsequently stabilized by intermolecular cross-links (7,8).

The importance of post-translational collagen cross-linking is in the pathogenesis of SSc is inevitable. The increase in pyridinoline cross-links is likely to be the result of increased activity of the enzyme responsible for the hydroxylation of the telopeptides, namely telopeptide lysyl hydroxylase (TLH). The highly increased expression of TLH in fibroblasts cultured from the fibrotic skin of SSc patients further reinforces the pathogenetic importance of the irreversible accumulation of cross-linked collagen in fibrotic tissues in these patients (9).

The microarray analysis of SSc revealed that these patients can be distinguished by unique gene expression signatures and besides the fibroblastic program, the results were indicative of cell proliferation, and immunological alterations (10).

Although, the pathogenesis of the disease is still unclear, the immunological damage can be explained by the increased T-cell activation. Activated T-helper lymphocytes secrete various fibrosis-related cytokines, such as IL-1, IL-4, IL-13, TGF-β, as well as interferon-gamma (IFN-γ), leading to fibrobyte migration, and eventual collagen deposition. In parallel, activated T-cells interact with B-lymphocytes, leading to B-cell proliferation and differentiation into plasma cells (11).

The overt humoral immune responses generate autoantibodies, including anti-topoizomerase I, as well as further pro-inflammatory/fibrogenic cytokines, resulting in, again, fibroblast activation and vascular damage (11).

Unfortunately, SSc is still non-curable, and in many instances even to delay the disease progression is a challenge. Life-threatening complications may develop due to acute renal insufficiency (scleroderma’s renal crisis) or pulmonary hypertension.

3. THERAPEUTIC APPROACHES IN SYSTEMIC SCLEROSIS

Generally, the treatment modalities in SSc are targeting the following four components in the pathogenesis: immune-modulating agents aiming to decelerate damaging, autoimmune processes; treatment, improving rheological parameters; anti-fibrotic agents; also various symptomatic therapeutic possibilities. Recently, novel treatment alternatives have been introduced, namely autologous stem-cell transplantation and extracorporeal photopheresis, which may open new avenues and improve the quality of life of SSc patients.

3.1. Immune-modulating treatment

Since various immune-competent cell types are involved in the pathogenesis of SSc, therapies have been developed, targeting a wide array of cellular and humoral immune responses. Corticosteroids are still the basis of treatment for most autoimmune diseases and in SSc, the administration of the medication has been shown to improve both the skin fibrosis or organ involvement (12). In contrast, it has been described that high-dose corticosteroid application (≥ 15 mg/day) may contribute to the development of renal crisis (13). It is of utmost importance to emphasize that in general, corticosteroid treatment is a double-edged sword; although theoretically it is beneficial in SSc, its therapeutic use is limited, since it can induce renal crisis. In SSc treatment, glucocorticosteroids can be used in patients with alveolitis, pericarditis, or associated myositis.

Besides glucocorticosteroids, methotrexate, the alkylating agent, cyclophosphamide, as well as cyclosporine A/tacrolimus, antagonizing calcineurin, an important enzyme in T-cell receptor signaling have been introduced (14). On the other hand, although Cyclosporine A via the reduction of IL-2 secretion can diminish T-cell activation and proliferation, it can cause glomerular sclerosis. This phenomenon raises the possibility that Cyclosporine A can induce fibrosis, presumably not just in the glomerular apparatus, but in other organs, organ-systems as well. Consequently, Cyclosporine A is used with limitations in the treatment of SSc, due to its dangerous side effects. Sirolimus, also known as rapamycin is used in patients with SSc and inhibits the response to interleukin-2 (IL-2) and thereby blocks activation of T- and B-cells. In contrast, Tacrolimus inhibits the production of IL-2 (Table 1).

3.2. Medications, affecting rheological parameters

Another therapeutic intervention in SSc is to improve rheological parameters and therefore increase circulation both in the skin and internal organs. The periodic vasospasm episodes finally lead to irreversible morphological changes and vascular damage. Accordingly,
endothelin receptor antagonists, phosphodiesterase-inhibitors, pentoxifyllin, prostaglandin I2 (PGI2/prostacyclin), calcium-channel blockers, as well as α1 adrenergic receptor antagonists (Prazosin) and 5-hydroxytryptamine (5-HT2A) (serotonin) receptor antagonists (Ketanserine) have been shown to be effective in this group (14). These agents improve rheological parameters by increasing vasodilation, also can act through the improvement of erythrocyte-flexibility. Recently, novel drug developments are targeting endogenous nitrate release, which does not lead to quick vasodilation and subsequent hypotonia, but initiate a continuous, modified release, which may secondarily alter transit and nutrient absorption. The gastrointestinal symptoms include gastro-esophageal reflux and dysphagia, therefore antagonists are of pivotal importance in the disease management, namely histamine 2 receptor antagonists (H2RA) and proton pump inhibitors (PPI). Gastroaesophagus, can be found in approximately 50% of patients. Severe small bowel disease can present as chronic intestinal pseudo-obstruction with distended loops of the small intestine, bacterial overgrowth, impaired absorption and progressive development of nutritional deficiencies (17). Accordingly, a great variety of prokinetic agents are used in SSc.

4. NOVEL IMMUNE-MODULATING APPROACHES

4.1. Autologous stem-cell transplantation (ASCT) in systemic sclerosis (SSc)

Patients, who are candidates for autologous stem-cell transplantation (ASCT) have rapid disease progression, including significant deterioration of skin symptoms and incipient kidney and/or lung involvement. Until now, approximately one hundred patients with SSc have gone through the transplant procedures in the main European and North American centers. The most frequently used conditioning protocol was high-dose cyclophosphamide (HDC) (200 mg/kg), along with anti-thymocyte globulin (ATG) and/or total body irradiation. T-cell ablation by CD34+-selection seemed to have an advantage in the treatment results. Previously, transplant-related mortality was over 10%, fortunately it has been improved to 2.5% in the recent years, due to stringent patient selection. An improvement of 25% or more in the skin score (measured by the modified Rodnan method) was reported in 70% of the patients following transplantation. Furthermore, lung function stabilized in most of the cases and renal function generally remained stable. After a follow-up period up to 60 months, 35% of the patients showed sustained improvement of the disease, while 25% progressed only after a transitional remission. Based on the favorable results of phase I/II studies (18-20), randomized, controlled studies were launched. The ASTIS trial is still running and tries to determine the superiority of ASCT over pulse cyclophosphamide treatment alone (control arm) (21-25).

Along with conventional treatment modules, ASCT by the beneficial effect of the repopulated, immunologically re-programmed, naïve stem cells could
Pathogenesis and therapy of SSC

play a significant role in the future management of SSC, leading to a better quality of life of these patients (26).

4.2. Extracorporeal photochemotherapy in systemic sclerosis (SSc)

Similar to plasmapheresis, extracorporeal photochemotherapy (photopheresis or ECP) is based on apheresis technology. The extracorporeal exposure of isolated peripheral blood mononuclear cells (PBMCs) to 8-methoxypsoralen (8-MOP) and ultraviolet (UV)A light is followed by reinfusion of the treated cells (27). Despite the efficiency of this procedure and the fact that ECP is in the focus of researches for a long time, the biologic mechanism of its exact action, which leads to immune-suppression, is not clearly understood in detail. Approximately 2-5% of the total peripheral leukocytes during each procedure is exposed to the photoactive drug 8-MOP (28). 8-MOP, due to the UVA light covalently binds and crosslinks DNA, which damages cellular DNA, induces apoptosis in the majority of treated cells (29).

Another possible mechanism of action is that ECP induces a significant increase of CD4+CD25+ regulatory T-cell levels, presumably leading to the deceleration of autoimmune responses (30).

In addition, ECP causes a decrease in monocytoid dendritcid precursors and an increase in plasmacytoid dendritic precursors. This change is appeared to be associated with a shift in the cytokine profile of cultured T cells from IL-2 and IFN-γ producing T helper (Th)1 cells to IL-10 producing Th2 cells (31).

Moreover, ECP leads to the increased expression of surface antigens by autoreactive T cells recognized by suppressor CD8+ T cells (32).

Photopheresis has been shown to induce significant improvement of skin and joint involvement in patients with scleroderma of recent onset (33), yet further multi-center studies are required to assess the real value of this procedure in SSC.

5. CONCLUDING REMARKS

In the pathogenesis of SSC several pathological processes simultaneously lead to disproportional fibrosis, vascular damage and organ failure, therefore the complex management of the disease, targeting these processes in parallel is pivotal for the more favorable disease outcome in SSC. Novel therapeutical approaches, namely ASCT and ECP can aid in the modern disease management, leading to sustained, better quality of life of these patients.

6. REFERENCES


Pathogenesis and therapy of SSC


**Key Words:** Systemic Sclerosis, Pathogenesis, Therapeutical Possibilities, Review

**Send correspondence to:** Peter Szodoray, Immunobiological Laboratory, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway, Postal address 1105 Blindern, N-0317 Oslo, Norway, Tel: 0047-22-851155; Fax: 0047-22-851278; Email: szodoray@gmail.com

http://www.bioscience.org/current/vol2E.htm