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Diffuse Systemic Sclerosis: Evolution in Treatment

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ABSTRACT

Systemic sclerosis (SSc) is a chronic multisystem autoimmune disease with wide variety of clinical presentations which makes its treatment challenging for clinicians. The aim of therapy is to decrease disability and preventing life-threatening organ involvement. Treating patients at an early stage of diffuse systemic sclerosis with proper agents will improve outcomes if initiated before an inflammatory process becomes irreversible. Immunosuppressive therapies with D-penicillamine, methotrexate (MTX), cyclophosphamide and others have been used commonly as classic treatment. Deeper knowledge of the immunopathogenesis of SSc has initiated a new era in treatment of diffuse systemic sclerosis. One of the new areas is biologic therapy including rituximab, imatinib, fresolimumab and others. Studies in biologic therapy have revealed significant improvement among patients with diffuse systemic sclerosis. Also, over the last two decades another challenging area has been introduced with hematopoietic stem cell transplantation which might change the future of systemic sclerosis. This review emphasizes that there are still unmet needs to achieve effective treatment in diffuse SSc and to reach this goal more studies need to be conducted.

KEYWORDS

Diffuse Systemic Sclerosis; Scleroderma; Treatment.

INTRODUCTION

Systemic sclerosis is a multisystem disease characterized by immunologic abnormalities, vascular hyperreactivity and fibrotic changes. The clinical manifestation of SSc is diverse in severity and extent of skin and internal organ involvement including skin thickening, Raynaud`s phenomenon, renal crisis, pulmonary artery hypertension, pulmonary fibrosis and etc [1].

SSc is a progressive disease with a high level of morbidity and mortality. The major contributor is fibrosis and the interaction of immune mediators and other growth factors with fibroblasts in responsive tissues, results in increased precipitation of Extracellular matrix (ECM) in the skin and internal organs.

The cornerstone of scleroderma treatment is prevention of the fibrotic reaction at an early stage of disease before it becomes irreversible. Immunosuppressive therapies with D-penicilliamine, methotrexate (MTX), cyclophosphamide, cyclosporine, mycophenolate mofetil and others are classic treatment of SSc and have been commonly used to regulate the inflammatory phase of disease in patients with progressive, early-stage disease. Currently, by better understanding the pathoimmunology of SSc which signifies the role of T-cell, B-cell and cytokines in activation of fibroblasts, a new era of study has initiated including: 1. Biologic therapies which interfere with specific cells or pathways that are involved, 2. Hematopoietic stem cell transplantation which has opened a new window in the future of scleroderma.

Natural History and Pathogenesis

Systemic sclerosis is a heterogeneous autoimmune disease with wild prevalence of 50-300 per million persons per year

based on geographic distribution [2, 3]. More than 40 years ago, the five-year survival rate was 50% in patients with no evidence of lung, heart, or kidney involvement. In patients with internal organ involvement the five-year survival rate was as low as one third, and development of acute renal disease resulted in death within 6 months. Currently, patients with scleroderma have significant improvements in quality of life compared to the past, and studies have revealed a five-year survival rate of 80-90% and ten-year survival rate of 70-80%. This improvement owes to recent completed and ongoing studies. Kidney, cardiac, and pulmonary dysfunction still are major concerns that limit survival [4].

Immunopathogenesis of SSc has been characterized as chronic infiltration of mononuclear cell in damaged tissue, dysregulation in production of growth factors and cytokines, and autoantibodies generation [5, 6].

The role of T lymphocyte is essential in driving inflammatory response and autoantibody generation [7]. CD4+ and CD8+ T cell subsets have been identified in affected tissue. In early stages of SSc, CD8+ T lymphocytes have been more predominant than CD4+ T cells in skin, whereas in late stages of disease the major involved cells are CD4+ T lymphocytes indicating the role of CD8+ T lymphocytes in early stages of the disease [8].

Activated B-cell signature has been detected in skin and lung of patients with systemic sclerosis, with overexpression of cell-surface markers of CD19 and CD21, costimulatory molecules including CD80 and CD86, and B-cell activating factor [9-12]. Function of B cell is regulated by CD19 and CD21 [13]. Overexpression of CD19 triggers production of autoantibody and fibrosis [14, 15]. Therefore, B cell depletion might inhibit autoantibody production and fibrotic changes.

There is a broad variety of mediators and cytokines which are produced by immune system and have been proposed to have significant roles in the inflammatory and fibrotic processes of SSc [16, 17]. Abnormality of cytokines levels as TGF-β, TNF-α, IL-6, IL-10, IL-17, IL4 and IL-13 have been detected in the serum and involved tissues of patients with systemic sclerosis. These cytokines stimulate fibroblasts to produce excessive collagen and accelerate fibrotic process [18-22].

Some studies have reported an association between severity of skin thickening and decreased survival where improvement of skin thickening has resulted in a better survival in patients with systemic sclerosis [23-26]. This has led recent clinical trial studies to employ skin thickening as the primary end point. Because of high variability in clinical manifestations, treatment of scleroderma has become challenging and several new treatment options have been introduced [27].

Methotrexate (MTX)

MTX is an analog of folic acid and has anti-inflammatory and immune-modulatory effects which can inhibit some cytokines including IL-1, IL-2, and IL-6.

A study by Van Den Hoogen; a randomized double-blind trial compared the efficacy of MTX vs placebo in the treatment of SSc. Twenty nine patients were enrolled; 17 in MTX group and 12 in placebo group and they were followed for 24 weeks. There was an improvement in total skin score (TSS) in patients treated with 15mg MTX weekly compared to placebo group (P=0.06). After 24 weeks, patients in MTX group and placebo group who did not have a good response underwent an increase of MTX to 25mg and switching to MTX, respectively. This study followed 22 patients (9 patients from placebo group and 13 patients from MTX group) for 24 more weeks. Patients were assessed at 48 weeks and a significant improvement of TSS was reported in patients treated with MTX in comparison to baseline (P=0.04) [28].

In a study by Sumanth, 33 patients were treated with 15-mg single oral dose of Methotrexate (MTX) followed by 15 mg/week of MTX for six months. The modified Rodnan skin scoring (mRSS) was used to assess the severity of skin involvement. Twenty five patients completed the 6 months evaluation and there was non-significant improvement in skin score after 6 months (P=0.135). Eight of these 25 patients continued the treatment with MTX for six more months and a significant improvement in mRSS compared to baseline was reported (14.5 ± 9.6 vs 18.3 ± 9.3, respectively) (P=0.027) [29].

In a study by Pope, a double blind, parallel trial 71 patients with early diffuse scleroderma (onset< 3 years) were compared in 2 groups; 35 patients were treated with Methotrexate and 36 patients were treated with placebo for one year. The mean MRSS in placebo group and MTX group at baseline were 27.4 ± 2.0 and 27.7 ± 2.0 respectively (P<0.91). After 1 year of treatment the result was in favor of MTX but was not statistically significant. (MRSS was 26.3 ± 2.1 vs 21.4 ± 2.8 in placebo group vs MTX group respectively) (P<0.17) [30].

In a study by Van Den Hoogen which evaluated low dose Methotrexate for treatment of SSc, skin improvement has been reported in most patients within six months of treatment [31].

D-penicillamine

D-penicillamine is a copper chelator which has immune-modulatory effects via reduction of T-cells, IL-1 and cross-linkage of collagen.

In a cohort study by Drek, efficacy of D-penicillamine in treatment of rapidly progressive diffuse cutaneous systemic sclerosis was evaluated. Eighty four patients with the onset of cutaneous manifestations less than 24 months before starting D-penicillamine were treated with median dose of 750 mg/

day D-penicillamine. The average duration of treatment with D-penicillamine was 29.2 ± 5.5 months and there was a statistically significant improvement of skin involvement. (mRSS was 19.9 ± 2.1 before starting D-penicillamine vs 13.9 ± 2.5 at the end of study)(P<0.01) [32].

A double blind, randomized, controlled clinical trial by Clements compared high dose (750-1000 mg/day) vs low dose (125 mg every other day) D-penicillamine in treatment of early (≤ 18 months) diffuse systemic sclerosis. One hundred thirty four patients entered the study and finally 68 patients (32 high dose and 36 low dose) completed 2 years of study. The mRSS at baseline was 20.4 ± 10.3 in high dose group and 19.9 ± 6.6 in low dose group. The reduction of mRSS in each group at the end of two years study was not significantly different (4.8 ± 10.3 points in high dose group vs 6.9 ± 8.4 points in low dose group)(P=0.384) which suggests it is not necessary to use a high dose of D-penicillamine in treatment of systemic sclerosis [33].

In a 36-month prospective study by Sattar, Sixteen patients with diffuse systemic sclerosis treated with D-penicillamine had significant skin improvement (P<0.001) [34].

Cyclosporine

Cyclosporine is an immunosuppressive agent which reduces T-lymphocyte activity.

In a study by Clements, a significant improvement of skin involvement (P<0.001) was reported in ten patients with systemic sclerosis (onset less than 5 years) who were treated with cyclosporine A [35].

The first retrospective study of the use of cyclosporine and/or tacrolimus in a routine clinical setting was evaluated by Morton in sixteen patients. The response to treatment was based upon a combination of the patient`s opinion and the physician`s general assessment. The mean duration of disease was 8.1 years and 14 of the 16 patients had been treated with immunosuppressants prior to enrollment in this study. Eight patients had been started on tacrolimus who had not responded adequately or who had developed side-effects while on cyclosporine. Thirteen patients had stopped cyclosporine because of side-effects and received medication for approximately 8 months. Only three patients continued with cyclosporine for 35, 528 and 383 days, respectively. The most common side-effect of cyclosporine was hypertension [36].

In a study by Filaci on nine patients who were treated with cyclosporine A at 2.5 mg/kg/day for 3-5 years, a statistically significant improvement of skin involvement after two and three years of treatment was noted compared to baseline (P=0.03 and P = 0.01 respectively) [37].

Mycophenolate Mofetil (MMF)

MMF has anti-inflammatory and anti-proliferative activities which can inhibit lymphocyte proliferation. It also reduces transforming growth factor β expression.

A retrospective study by Nihtyanova compared 109 patients treated with mycophenolate versus 63 patients receiving other immunosuppressive medications. After 5 years of treatment, the study showed no significant difference in skin improvement according to mRSS. (Median mRSS was 26 in both groups at baseline and after 5 years was 11 and 15 in MMF group versus control group respectively) [38].

A prospective observational study by Mendoza evaluated 25 patients with early systemic sclerosis (onset < 24 months) whom were treated with MMF. After 18.2 ± 8.73 months of treatment with a median dose of 2000 mg/day, there was a change in mRSS from 24.56 ± 8.62 to 14.52 ± 10.9 which represented a statistically significant improvement of skin involvement (P=0.0004) [39].

A prospective open-label study by Derk which evaluated 15 patients with diffuse systemic sclerosis whom were treated with mycophenolate mofetil for one year, reported a significant improvement in mRSS (P<0.0001) [40].

Studies reported by Herrick and Kotroumpas showed non-significant improvement of mRSS following treatment with mycophenolate mofetil in patients with systemic sclerosis [41, 42].

A study by Le reported that improvement in mRSS in patients treated with mycophenolate for 1 year was significantly less than patients treated with D-penicillamine (P<0.001) [43].

Cyclophosphamide

Cyclophosphamide (CYC) is an alkylating agent with anti-inflammatory and immunosuppressive properties which can reduce B and T lymphocytes.

In a randomized, unblinded trial by Nadashkevich, 30 patients with systemic sclerosis were treated with cyclophosphamide (CYC) (2mg/kg daily) and in another group 30 patients were started on azathioprine (AZ) (2.5 mg/kg daily). After 18 months, there was a statistically significant improvement in mRSS in CYC group (from 14.7 ± 1.06 at baseline to 5.23 ± 0.5 at 18 months) which was not seen in AZ group [44].

In a study by Pakas, twelve patients were treated with monthly IV cyclophosphamide plus low dose of prednisolone (< 10 mg/day), while another 16 patients were started on monthly IV cyclophosphamide in combination with high dose of prednisolone (1 mg/kg/day for 4 weeks, then reducing dose). After 12 months, in high dose prednisolone group a significant improvement of skin involvement (P=0.01) was reported which was not detected in the group with low dose prednisolone [45].

A study by Valentini on patients with early systemic sclerosis

(onset less than 24 months) treated with intravenous cyclophosphamide 500 mg per pulses and 10 mg prednisone equivalent, reported statistically significant improvement of mRSS after 6 and 12 months of treatment compared to baseline. (P=0.002 and P=0.002 respectively) [46].

TARGETED THERAPY

Rituximab (RTX)

Rituximab is a monoclonal antibody against CD20 which can cause a depletion in peripheral B cells.

In EUSTAR study; a multicenter, case control, observational study, 63 patients with systemic sclerosis (limited SSc and diffuse SSc) were treated with Rituximab. RTX was mainly administered as 2 infusions of 1000 mg during two weeks and 65% of patients also received DMARDs as co-treatment. Thirty five patients of RTX group who had diffuse SSc at the time of enrolment showed a statistically significant improvement of mRSS after six months of follow-up compared to baseline (17.7 ± 1.6 vs 22.1 ± 1.6) (P = 0.0005). Among these 35 patients with diffuse systemic sclerosis, 25 patients had severe diffuse systemic sclerosis (mRSS ≥ 16). To evaluate the response in RTX group versus control group (who did not receive RTX), these 25 patients with severe SSc were compared to control group. At follow-up, the results showed a more significant improvement in mRSS in RTX group compared to controlled group (6.3 ± 1.4 units vs 1.9 ± 1.0 units respectively) (P=0.02). In this study, the adverse effects which were observed in RTX group included: fatigue, infections, nausea, rigour, renal and cardiac problems, Serum sickness and hypersensitivity [47].

In a 1-year randomized study by Daoussis, 8 patients with systemic sclerosis were treated with two cycles of rituximab at baseline and after six months (4 weekly infusions of 375 mg/m2 were given as a cycle) plus conventional treatment and six patients were started on conventional treatment only. After 12 months, there was a statistically significant improvement in mRSS in RTX group (from 13.5 ± 6.84 at baseline to 8.37 ± 6.45 at 12 months) (P = 0.0003) which was not seen in control group. The difference of mean mRSS between two groups at baseline was not significant (13.5 ± 6.84 vs 11.5 ± 2.16 in RTX and control group respectively) (P =0.50) [48].

In another multicenter, open-label study by Daoussis; 33 patients with systemic sclerosis received at least two cycles of RTX (each cycle included four weekly infusions of RTX 375 mg/m2) and were compared to 18 patients who treated with conventional treatment alone. Thirteen patients in RTX group also received DMARDs as co-treatment. At one year follow-up, all of the patients in both groups were evaluated. At this follow-up there was a statistically significant decrease of mRSS in RTX group compared to baseline (from 14.72 ± 10.52 at baseline to 8.83 ± 7.83 at one year) (P<0.01). Also comparison of two groups at one year follow-up showed a better improvement of mRSS in favor of RTX group which was statistically significant (P=0.002). During the next follow-up sessions including follow-up at second year and afterwards there was a decrease in number of patients in both groups because of physician`s decision or loss of follow-up, but there was still a better response in RTX group compared to control group [49].

Tocilizumab

Tocilizumab is an inhibitor of interleukin 6 receptor.

A phase II, randomized, controlled trial by Khanna evaluated safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis. In this study 87 patients were enrolled. Forty three patients were treated with tocilizumab and forty four patients were started on placebo. There was some improvement in mRSS in favor of tocilizumab which was not statistically significant. Severe infection was reported with higher incidence in tocilizumab group (16% in tocilizumab group compared to 5% in placebo group). Also one death related to treatment with tocilizumab was reported [50].

Fresolimumab

Fresolimumab is a monoclonal antibody that targets all isoforms of TGF-β.

In a study, Rice evaluated the effect of fresolimumab in SSc. Fifteen patient were enrolled and mid forearm skin biopsies were obtained before and after treatment to assess expression of the TGF-β regulated genes and dermal infiltration of myofibroblasts. Seven patients received two rounds of 1 mg/kg doses of fresolimumab, and eight patients received one round of 5 mg /kg dose of fresolimumab. There was a rapid improvement in mRSS which was statistically significant (P<0.001). Also this study showed reduction in expression of TGF-β regulated gene following treatment which strongly signifies effect of TGF-β in pathogenesis of SSc [51].

Imatinib

Imatinib is a tyrosine kinase which inhibits producing of PDGF and TGF-β.

A phase I/IIa open-label pilot study by Khanna assessed safety and efficacy of imatinib in treatment of SSc. Twenty patients with systemic sclerosis with mean disease duration of 54 months were started on Imatinib for one year. Imatinib was given 100 mg daily as initial dose and was titrated up by 100 mg every two weeks (Up to 600 mg daily). Twelve patients completed the treatment. There was loss of follow up for one patient and side effects including fatigue, edema, gastrointestinal and renal problems, and rash happened to seven patients, so treatment was discontinued. In 12 patients who completed one year of treatment there was a statistically significant improvement of mRSS (3.9 units) compared to mean mRSS at baseline (18.7 ± 10.1) (P<0.001) [52].

Intravenous immunoglobulin (IVIG)

IVIG has immunomodulatory activity and might inhibit cytokines and mediators which are involved in pathogenesis of systemic sclerosis.

In a study by Levy in 2000, three patients with systemic sclerosis were treated with IVIG 2 mg/kg/month. In one patient after three rounds of treatment, renal failure happened and treatment was discontinued, but another two patients received six rounds of IVIG. In all three patients a large decrease in mRSS following treatment was reported [53].

In another study by Levy in 2004, fifteen patients with systemic sclerosis were started on IVIG 2mg/kg/month. Eleven patients received 6 rounds of IVIG, three patients underwent 4 rounds and one patient was treated with 3 rounds. There was a statistically significant improvement in mRSS (10 ± 5.9 units) compared to baseline ($P < 0.001$) [54].

Mesenchymal Stem Cell-based Therapy (MSC)

MSC has an immunosuppressive effect that results in inhibition of B-lymphocytes and T-lymphocytes [55, 56].

Recently 2 cases were reported whom were treated with MSC. Both patients had refractory, progressive scleroderma that before enrollment in this study they had been treated with a recommended standards of care. Methods: The 2 patients underwent 4 sessions of plasmapheresis, followed by 1 g of rituximab and then infusion of Allo-MSC intravenously. The clinical assessment tool used was European Scleroderma Study Group (EsSG) activity index. The 2 patients were 28 and 30 years of age, EsSG activity index score at baseline was 9.5 and 9.5 respectively. The EsSG activity index score after 1 year of treatment was 3.5 and 1.5 respectively. Both patients reported significant improvement in mobility, functional capacity and quality of life. Both patients received a second round of Allo-MSCs in 12 and 16 months respectively, when their disease progressed, and they declared significant improvement again [57].

Autologous Hematopoietic Stem Cell Transplant (HSCT)

The rationale of HSCT is prevention and even reverse of damage from autoimmune diseases [58].

Since 2001, 3 prospective, controlled trials have been conducted to evaluate efficacy, safety and long term side effects of Autologous HSCT in patients with SSc which called ASSIST, ASTIS and SCOT.

ASSIST Trial

The American scleroderma stem cell versus immune suppression trial was a phase II trial in North America which assessed the efficacy and safety of autologous non myeloablative HSCT vs monthly pulse intravenous cyclophosphamide in patients with SSc [59].

In ASSIST trial, 19 patients were enrolled and randomly allocated in 2 groups. Ten patients received HSCT and 9 patients received 6 monthly pulses of cyclophosphamide as a control group. All 10 patients who received HSCT showed improvement in mRSS compared to control group after one year. Also there was an increase in mean predicted FVC and TLC in the HSCT group compared to decreased FVC and TLC in the control group. In the control group, who received cyclophosphamide, seven of nine patients underwent HSCT after mean of 14 months of initiation of study. No death had been reported until 2011 [60].

ASTIS Trial

The autologous stem cell transplantation international scleroderma trial is a multicenter, randomized, phase III clinical trial which studied 156 SSc patients in 28 centers in Europe and one center in Canada [61]. The primary endpoint of study was event-free survival. 156 patients were allocated in 2 groups, 79 patients in HSCT group (high dose immunoablation followed by HSCT) and 77 patients in control group (12 monthly pulses of IV cyclophosphamide). As of 2012, early treatment-related mortality in the transplant group was 10.1% while the final result revealed a better long-term event-free survival (survival free of organ failure) in the HSCT group [60].

SCOT Trial

The scleroderma: cyclophosphamide or transplantation trial; a randomized, controlled phase III trial was conducted in North America to compare high-dose immunosuppressive therapy and hematopoietic cell transplantation to monthly pulse cyclophosphamide [62]. This study used total body irradiation (TBI) and equine anti-thymocyte globulin in conditioning phase which defers with two other studies, ASTIS and ASSIST. This study is still ongoing [60].

CONCLUSION

By today, plenty of studies have been conducted to better understand the pathogenesis of scleroderma. These studies have brought new treatment options for diffuse systemic sclerosis. As we reviewed here, most of them have evaluated the efficacy of a single agent and reported significant therapeutic response while there is lack of enough studies to compare two different treatment options in diffuse SSc. More studies are needed to evaluate efficacy of current agents together and narrowing down our treatment options. New era in treatment with HSCT have started which might bring new hopes for patients with diffuse SSc and organ involvement, but more investigations in this field are necessary to answer which patient will get more benefit of HSCT and how to decrease treatment-related mortality.

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CONFLICT OF INTERESTS

Authors declare no conflict of interest.

ABBREVIATIONS

MTX: Methotrexate.

SSc: Systemic sclerosis.

ECM: Extracellular matrix.

IL: Interleukin.

TSS: Total skin score.

mRSS: modified Rodnan skin scoring.

MMF: Mycophenolate Mofetil.

CYC: Cyclophosphamide.

AZ: Azathioprine.

TGF-β: Transforming growth factor beta.

PDGF: Platelet-derived growth factor.

IVIG: Intravenous immunoglobulin.

MSC: Mesenchymal Stem Cell.

HSCT: Hematopoietic Stem Cell Transplant.

FVC: Forced vital capacity.

TLC: Total lung capacity.

TBI: Total body irradiation.

DMARDs: Disease-Modifying Antirheumatic Drugs.

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