

Recent advances in the diagnosis and treatment of systemic sclerosis

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ABSTRACT

Systemic sclerosis (SSc) is a multisystem autoimmune disease characterized by widespread vascular injury and progressive fibrosis of the skin and internal organs. The involvement of internal organs results in significant morbidity and mortality of SSc patients with cardiopulmonary involvement being the leading cause of SSc-related deaths. The management of SSc patients remains a challenge because therapeutic options are rather limited and no therapy has definitively shown a disease-modifying effect. A significant progress that has recently been made in the understanding of the SSc pathogenesis contributed to the introduction of new therapeutic options. Preliminary clinical studies have yielded promising results for mycophenolate mofetil, anti-CD20 antibodies, and stem-cell in the treatment of SSc. Multicenter cohort studies help understand the natural history of SSc, which leads to improvement in the care of SSc patients. The major objective of those studies is to establish the screening strategies for early diagnosis and, subsequently, to introduce appropriate management concerning specific organ involvement in SSc as well as to formulate specific treatment recommendations.

Introduction Systemic sclerosis (SSc) is a multi-system autoimmune disease characterized by widespread vascular injury and progressive fibrosis of the skin and internal organs. Internal organ involvement results in increased mortality of SSc patients, with cardiopulmonary complications being the most frequent causes of disease-related deaths.¹ The management of patients with SSc is challenging for several reasons. There is no universal disease-modifying drug in SSc, and only few therapies have shown modest benefits with regard to some specific organ pathologies.² Clinical heterogeneity of the disease, resulting in different clinical patterns and prognosis in individual patients, makes the management of SSc even more difficult.

In the last decades, SSc attracted more attention from both scientific community and clinicians. Intensification of research, supported by international initiatives, such as the European League Against Rheumatism (EULAR) Scleroderma Clinical Trials and Research (EUSTAR) group, improved our knowledge of the pathogenesis and clinical course of SSc. This, in turn, led

to the introduction of new promising therapies and allowed to design more individualized management strategies. On the other hand, a close cooperation with experts in other related disciplines, such as cardiology or pulmonology, has broadened diagnostic and therapeutic armamentarium required for improving the diagnosis and treatment of SSc-related organ complications.

This review presents the most important achievements in the diagnosis and treatment of SSc in recent years.

Advances in diagnosis Diagnosis of SSc, like in the case of other connective tissue diseases, is based on the combination of clinical and/or laboratory features. The classification criteria of SSc, which have been used until now, were developed by the American College of Rheumatology (ACR) in 1980, and included symmetrical thickening of the skin of the fingers (with or without the involvement of more proximal skin areas), lung fibrosis, and loss of tissue of the finger pads.³ Those clinical features, although characteristic for SSc, represent advanced tissue injury. Indeed,

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it has been recognized that the 1980 ACR criteria are not sensitive enough to diagnose patients with early SSc, in particular those with a limited form of the disease. The discoveries in the field of SSc-specific microangiopathy and autoantibodies, together with a better understanding of the natural course of the disease, gave rise to efforts to develop new classification criteria for SSc, including a recent joint initiative of the ACR and the European League against Rheumatism (EULAR).⁴ As a result of the latter initiative, the preliminary set of the new ACR/EULAR classification criteria for SSc had been formulated and were announced as a late-breaking abstract at the ACR Congress in November 2012 in Washington, United States (unpublished data). Apart from skin and lung involvement characteristic for SSc, the new ACR/EULAR classification criteria also include the presence of Raynaud's phenomenon, telangiectasia, abnormal nailfold capillaries, and SSc-related autoantibodies. The sensitivity and specificity of the new ACR/EULAR criteria in diagnosing SSc were higher compared with the previous ones. The new criteria can be supported by epidemiological studies and clinical trials after the approval by the ACR and EULAR.

Early identification of SSc patients is of great importance from both scientific and clinical points of view. Studies performed in patients at the early stage of the disease might foster research on the processes that play a crucial role in the pathogenesis of SSc. Moreover, the identification of patients at an early disease stage allows to include them into regular screening strategy aimed at early diagnosis of severe organ involvement. Indeed, the early diagnosis of potentially fatal organ complications, particularly cardiopulmonary involvement, is considered of key importance in the management of SSc patients. Accordingly, screening programs consisting of regular clinical assessment together with pulmonary function testing, echocardiography, and lung radiology were developed and are recommended by the international guidelines, including quality indicators in SSc.⁵⁻⁹ As shown by recent analyses, the implementation of the screening programs into clinical practice resulted in improved identification of SSc patients with cardiopulmonary involvement and better identification of patients with less advanced lung disease.¹⁰⁻¹¹

Despite progress that has been made in this field, the early identification of patients with poor prognosis is still unsatisfactory, in particular due to significant clinical heterogeneity of SSc and specific SSc-related organ complications. The discovery of new biomarkers, which would improve early diagnosis, identify subjects at risk of severe organ involvement, is therefore considered an important goal of research in SSc.¹² Extensive studies performed in the past 2 decades, including gene expression analysis and proteomics, led to the identification of many potential candidates. So far, however, only the brain natriuretic peptide and its N-terminal cleavage product proved

clinically useful and have been included in the assessment of patients with pulmonary arterial hypertension (PAH).^{7,12} A number of other molecules have shown correlations with severity and/or activity of the overall disease process or specific organ pathologies in SSc. Many of these molecules represent the pathways involved in the pathogenesis of SSc, including the markers of blood vessel injury and regeneration, molecules involved in the regulation of immune/inflammatory response and/or connective tissue remodeling, such as angiopoietins, growth factors, chemokines, and cytokines together with the recently discovered members of the tumor necrosis factor (TNF)- α superfamily.¹³⁻¹⁷ Other molecules are associated with specific organ involvement, such as surfactant proteins, which are considered the markers of lung pathology.¹² However, further studies are needed to clarify their usefulness as biomarkers relevant in clinical practice.

Interesting findings have recently been reported by Pendergrass et al.¹⁸ who showed that particular patients with diffuse form of SSc have different profiles of gene expression in the skin. Based on their gene expression profile, patients could be divided into fibroproliferative, inflammatory, or normal-like subgroups. The gene profiles remained stable over time, further emphasizing the existence of pathological heterogeneity of scleroderma. Those findings, if confirmed in other populations of SSc patients, might be of vital importance for the future development of personalized therapy for SSc.

Advances in treatment Because of lack of universal disease-modifying therapies and significant clinical heterogeneity of the disease, management of SSc is based on the so called organ-targeted therapy.² This strategy consists of the application of specific drugs or treatment options depending on the presence of specific organ involvement. Therapies useful in treating SSc-related organ complications have been summarized in the EULAR recommendations for the treatment of SSc, which were published in 2009.¹⁹ In the last years, several other therapies showed promising beneficial effects in the treatment of SSc. Most recent advances in the management of scleroderma patients are reviewed below.

Treatment of systemic sclerosis-related vascular disease Vasculopathy is an important feature of SSc and involves both the peripheral and visceral vessels. PAH, developing due to obliterative angiopathy of the pulmonary arteries, is currently the leading cause of scleroderma-related deaths.¹ In the last decades, a significant progress has been made in the treatment of SSc-related PAH. As mentioned before, the development of screening programs improved the identification of patients with less advanced PAH.¹¹ This, in turn, enabled the early start of treatment, which is particularly important in SSc-related PAH because of its irreversible and progressive

nature.²⁰ The approval of endothelin receptor antagonists, phosphodiesterase-5 (PDE-5) inhibitors and new forms of prostacyclin analogues broaden the spectrum of drugs helpful in the treatment of PAH and opened way for combination therapy in patients who do not respond to therapy with single agents.^{7,21} Recent data indicate that advances in the management of scleroderma-related PAH, in particular early detection and sequential combination therapy of this devastating condition, may improve the survival of patients with SSc-related PAH.^{11,20}

New agents used for the treatment of PAH have also shown benefits in the management of some aspects of SSc-related peripheral vasculopathy. An unselective endothelin receptor inhibitor, bosentan, has proved effective in the prevention of new digital ulcers in patients with SSc.²² However, bosentan had no effect on the healing of pre-existing digital ulcers.²² Two recently published randomized controlled trials (RCTs) have indicated that PDE-5 inhibitors may improve SSc-related Raynaud's phenomenon.²³⁻²⁴ In an RCT involving 57 patients with a limited form of SSc, sildenafil proved effective in decreasing the frequency of attack of Raynaud's phenomenon in this patient population.²³ In another RCT involving 25 patients with SSc or mixed connective tissue disease, tadalafil significantly improved the frequency and severity of attacks of Raynaud's phenomenon and reduced the number of digital ulcers.²⁴ Moreover, small open-label studies indicate that sildenafil might improve the healing of digital ulcers in SSc.²⁵

Based on their efficacy in other vascular diseases, statins have recently gained attention as potential treatment for SSc-related vasculopathy. In an RCT, atorvastatin decreased the severity of Raynaud's phenomenon and the total number of digital ulcers in patients with SSc.²⁶ Along with the clinical benefit, an improvement in the serum markers of endothelial activation was also observed. However, these promising observations need to be confirmed in other RCTs involving different populations of SSc patients.

Vascular injury is not only a clinical problem in scleroderma patients but is also implicated in the pathogenesis of SSc. Therefore, it is hypothesized that therapies targeting vascular injury might have a potential disease-modifying effect. Whether vasoactive treatments can inhibit the development of SSc-related organ injury remains to be established.

Immunosuppressive therapy Immunosuppression is considered a cornerstone of therapy of diffuse progressive SSc and SSc-related interstitial lung disease (ILD). However, the evidence for efficacy of immunosuppressive drugs in treating SSc-related organ involvement is limited.² In the Scleroderma Lung Study-1 (SLS-1), the first big RCT including exclusively patients with ILD, a 12-month therapy with oral cyclophosphamide (CFX, given at a dose of 1–2 mg/kg/d) resulted in a significant

although clinically mild improvement in forced vital capacity (FVC; 2.5% of predicted in favor of CFX).²⁷ No significant effect on diffusing capacity of the lungs for carbon monoxide (DL_{CO}) could be demonstrated.

A post-hoc analysis of the results of the SLS-1 revealed that the mean (\pm standard deviation) annual decrease in FVC in 79 placebo-treated patients was 4.2% (\pm 12.8%) of predicted indicating that although the progression of lung fibrosis was generally mild, there is significant heterogeneity in the clinical course of ILD.²⁸ Patients with more severe fibrosis on high-resolution computed tomography (HRCT) of the lungs at baseline experienced a significantly greater decline in FVC at follow-up (7.2% \pm 11.8%) compared with those with less or no fibrosis (2.7% \pm 12.8% per year, $P < 0.05$).²⁸ These observations are in agreement with the results of the previously published cohort studies.⁵ Accordingly, in the SLS-1, the greater severity of lung fibrosis on HRCT of the lungs and worse dyspnea were independent predictors of response to CFX therapy.²⁹ Altogether, those observations indicate that treatment of ILD should be individualized. Aggressive treatment with CFX might be justified in patients with severe and/or progressive ILD, while in patients with less advanced and slowly progressive ILD less toxic therapies could be considered.

Several open-label studies published in the recent years indicate that mycophenolate mofetil (MMF) improves or stabilizes skin changes and/or lung function in patients with SSc. Those observations have been further confirmed by a retrospective analysis comparing clinical outcomes in 109 patients with diffuse SSc receiving MMF with 63 well-matched control cases treated with other immunosuppressive drugs including CFX, azathioprine, and antithymocyte globulin.³⁰ Patients treated with MMF less frequently developed clinically relevant ILD and had better 5-year survival compared with control cases. There was no significant difference between the 2 groups in terms of the change in the skin score or FVC.

In another recent study, Lee et al.³¹ compared the effect of MMF as first-line therapy in 98 diffuse SSc patients and progressive skin disease with the data of 533 historical controls from 3 RCTs investigating D-penicillamine, collagen, and relaxin in patients with diffuse SSc. MMF (1000 mg/d to 3000 mg/d for 12 months) improved the skin score compared with historical controls from RCTs. Lung function remained stable under MMF therapy. Similar results (stabilization of lung function over time) were shown in a meta-analysis of 6 open-label studies including 69 patients with ILD.³²

MMF was well-tolerated with side effects (mainly gastrointestinal disturbances, infections, or anemia) present in approximately one-tenth of the patients.³⁰⁻³² Thus, the available evidence indicates that MMF might be beneficial in treating skin and lung involvement in SSc patients. However, low numbers of SSc patients enrolled

in prospective studies and lack of randomization preclude firm conclusions. Following the promising results of these preliminary studies, an RCT aimed to compare MMF with CFX in patients with SLD (Scleroderma Lung Study-2) has been designed and is currently underway.

Stem cell transplantation Autologous hematopoietic stem cell transplantation (HSCT) has been proposed as a treatment option in patients with progressive SSc and/or internal organ involvement who do not respond to other therapies. Several studies evaluating the safety and efficacy of this treatment are currently underway in Europe and United States. In 2011, the results of the first RCT comparing HSCT with conventional CFX therapy was published.³³ A total of 19 SSc patients with diffuse skin disease and internal organ involvement or limited form of SSc and restrictive SLD have been studied. Ten patients from the HSCT group received conditioning with CFX (200 mg/kg intravenously) and antithymocyte globulin followed by stem cell infusion. The remaining 9 patients received standard CFX therapy consisting of 6 monthly infusions of CFX (1 g/m² per month). At 12 months, the frequency of clinical improvement, defined as a decrease in the skin score by at least 25% in patients with diffuse SSc or improvement of at least 10% in FVC in those with restrictive SLD, was greater in SSc patients who underwent HSCT (100%) compared with SSc patients treated with CFX alone (none, odds ratio = 110, 95% confidence interval: 14.04 – ∞, *P* = 0.00 001). Deterioration was observed in 8 of 9 SSc patients treated with standard CFX. Seven patients who deteriorated on standard CFX therapy subsequently underwent HSCT, which resulted in clinical improvement in all of them. None of the patients died during the study.

Although the results of this study indicate that severe immunosuppression followed by stem cell transplantation is beneficial compared with traditional immunosuppression, further studies involving the greater numbers of patients are needed to establish the role of this treatment strategy in the management of SSc. The results of such studies should be available soon.

Biological therapies In the last decade, several biological therapies have been approved for treating patients with connective tissue diseases such as rheumatoid arthritis or lupus erythematosus disseminates. So far, only few open-label studies have investigated the safety and efficacy of biological therapies in patients with SSc.³⁴

Since the transforming growth factor β (TGF- β) is considered to play the key role in fibrotic diseases, including scleroderma, inhibition of TGF- β appears to be a promising therapeutic strategy in SSc. Only 1 RCT evaluating the efficacy of TGF- β_1 -neutralizing antibodies has been published so far.³⁵ In this study, including 45 patients with early SSc (<15 months), recombinant

anti-TGF- β antibodies (CAT-192), given at a dose of up to 10 mg/kg, showed no significant effect on skin or other forms of SSc-related organ involvement. Other therapies targeting TGF- β -dependent pathways are currently studied in the experimental and clinical settings.

The TNF inhibitors have proved remarkably effective in several autoimmune or chronic inflammatory diseases including rheumatoid arthritis, psoriasis, or Crohn's disease. However, there are only few data regarding the use of anti-TNF therapies in patients with SSc. The safety and efficacy of infliximab, a chimeric anti-TNF- α antibody, was assessed in a 26-week open-label study involving 16 patients with diffuse SSc and progressive skin disease.³⁶ Infliximab given intravenously, at a dose of 5 mg/kg at weeks 0, 2, 8, 14, and 28, stabilized the skin score. There was no significant change in other clinical parameters as evaluated by either the scleroderma health assessment questionnaire or physician's global assessment. Eight patients (50%) discontinued infliximab prematurely mainly due to suspected infusion reactions. No death or unsuspected infliximab-related adverse events could be observed during up to 48-week safety follow-up.

In another report, including 18 patients with scleroderma and arthritis overlap syndrome, etanercept, a TNF receptor-Fc fusion protein, showed beneficial effects in the management of SSc-related joint disease.³⁷ Similarly, the results of a recent survey, concerning the experience with TNF blockers in SSc among experts associated within the EUSTAR group, indicated that improvement was seen mainly with arthritis, while the effect on fibrosis was variable.³⁸ The majority of respondents agreed that, due to limitations in the available evidence, TNF inhibitors should not be used or only used in clinical trials in SSc patients.

Based on strong experimental data indicating the key role of B cells in the development of fibrosis and following successful use in other connective tissue diseases such as rheumatoid arthritis or systemic lupus erythematosus, anti-CD20 antibody has recently been tried in the treatment of patients with SSc.³⁹ The results of small-size open-label studies showed that rituximab (anti-CD20 antibody) improved or stabilized the skin score and lung function tests in patients with diffuse SSc over time (TABLE).⁴⁰⁻⁴⁴ In general, rituximab therapy was safe with injection site reactions being the most common side effects. In addition to promising clinical findings, therapy with rituximab resulted in a significant histological improvement in skin samples including reduction of collagen deposition, depletion in myofibroblasts score and B-cell numbers, suggesting a potential disease-modifying effect of rituximab in skin fibrosis.⁴⁰⁻⁴¹ These highly encouraging results of preliminary studies make rituximab a promising therapy for SSc-related skin and lung disease. However, these data need to be confirmed by the results of RCTs.

TABLE Summary of studies evaluating the safety and efficacy of rituximab in patients with systemic sclerosis

Study	Duration, mo	Number of patients	Treatment	Major clinical effects	Adverse effects
Lafyatis ⁴⁰	6	15 dSSc of ≤18-month duration	RTX IV 1000 mg – days 0 and 15	stabilization in mRSS, PFTs, and HAQ	infusion reactions in 47% of the patients infections in 1 patient 1 SAE considered unrelated to RTX
Smith ⁴¹	6	8 dSSc of ≤4-year duration	RTX IV 1000 mg – days 0 and 15 ^a + MTX 15 mg/w	improvement in mRSS and disease activity score ($P < 0.05$) stabilization in PFTs, LVEF, SPAP, GFR, functional status and quality of life (HAQ, SF-36)	2 SAE considered unrelated to RTX
Bosello ⁴²	6	9 dSSc with progression of skin score despite CFX	RTX IV 1000 mg – days 0 and 15 ^a	improvement in mRSS, HAQ, activity index, severity index ($P < 0.01$) stabilization in PFTs	1 SAE considered unrelated to RTX
Daoussis ⁴³	12	14 SSc with SLD (randomized)	RTX IV 375 mg/m ² /w × 4, repeated after 6 months RTX + standard treatment ^b in 8 patients standard treatment ^b in 6 patients	improvement in FVC and DL _{CO} ($P < 0.05$ vs. controls) stabilization in mRSS ($P = 0.06$ vs. controls) HAQ improved in RTX group ($P < 0.05$ vs. baseline) and remained unchanged in controls ($P > 0.05$ vs. baseline)	1 respiratory tract infection
Daoussis ^{44,c}	up to 24 months	8 SSc with SLD	RTX IV 375 mg/m ² /w × 4, repeated at 6, 12, and 18 months (+ standard treatment ^b)	improvement in mRSS, FVC, DL _{CO} , and HAQ ($P < 0.05$ vs. baseline), heart and renal function remained stable	3 cases of infections 1 with leukopenia 1 mild infusion reaction

a 100 mg of methylprednisolone was given with each infusion of RTX

b standard treatment included low-dose of prednisolone and/or mycophenolate mofetil

c long-term extension of the study reported in 2010

Abbreviations: CFX – cyclophosphamide, DL_{CO} – diffusing capacity of the lungs for carbon monoxide, dSSc – diffuse systemic sclerosis, FVC – forced vital capacity, GFR – glomerular filtration rate, HAQ – health assessment questionnaire, IV – intravenously, LVEF – left ventricle ejection fraction, mRSS – modified Rodnan skin score, MTX – methotrexate, PFTs – pulmonary function tests, RTX – rituximab, SAE – serious adverse effects, SF-36 – 36-item short form health survey, SLD – scleroderma-related interstitial lung disease, SPAP – systolic pulmonary artery pressure

Considering the promising results obtained with anti-CD20 therapy, it could be hypothesized that other B-cell-targeting therapies might also be of interest in the treatment of SSc. Indeed, it has recently been shown that B-cell activators such as BAFF or APRIL are upregulated in SSc.^{16-17,39} Those factors may represent new promising therapeutic targets in SSc. Of note, atacicept, a recombinant fusion protein comprising the extracellular domain of the TACI receptor, which binds APRIL and BAFF, is currently under study in systemic lupus erythematosus.⁴⁵

Kinase receptor inhibitors Based on experimental and clinical evidence, kinase receptor inhibitors have been proposed as a treatment option in patients with severe SSc. Imatinib mesylate (Gleevec), a selective inhibitor of *c*-Abl kinase, has proved highly effective in treating chronic myeloid leukemia in humans and was shown to

inhibit skin and lung fibrosis in animal models.⁴⁶ In the last 2 years, several small RCTs evaluating imatinib mesylate in patients with SSc have been published showing highly variable results from very encouraging clinical improvements to lack of efficacy or toxic responses.⁴⁷⁻⁵⁰ Further studies are needed to clarify the role of imatinib mesylate and other kinase receptor inhibitors, such as dasatinib or nilotinib in the treatment of patients with SSc.

Summary Extensive clinical and experimental studies performed in the last decades improved our understanding of the pathogenesis of SSc as well as our knowledge about the clinical course of SSc-related organ pathologies. This, in turn, led to advances in the management of SSc, including the introduction of screening strategies aimed at early detection of SSc-related organ involvement and the development of new treatments of

SSc-related pathologies. Early identification and management of SSc-related pathologies resulted in improved survival of SSc patients. A number of new agents are currently being investigated in clinical and experimental studies. Once we fully recognize the heterogeneity of the disease and markers of prognosis, we will be able to individualize the therapy, which will help achieve the best therapeutic effect with minimum toxicity.

Despite the progress that has recently been made in the treatment of SSc, the management of scleroderma patients remains challenging. Further efforts are required to develop more effective therapies of the disease.

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Postępy w diagnostyce i leczeniu twardziny układowej

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SŁOWA KLUCZOWE

diagnostyka, leczenie,
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twardzina układowa

STRESZCZENIE

Twardzina układowa (*systemic sclerosis* – SSc) jest układową chorobą o podłożu autoimmunologicznym charakteryzującą się uogólnionym uszkodzeniem naczyń krwionośnych oraz postępującym włóknieniem skóry i narządów wewnętrznych. Zajęcie narządów wewnętrznych jest powodem wysokiej śmiertelności chorych na SSc, a powikłania ze strony płuc i serca stanowią obecnie główną przyczynę zgonów spowodowanych SSc. Leczenie chorych na SSc jest prawdziwym wyzwaniem ponieważ możliwości terapeutyczne są ograniczone i nie ma uniwersalnych leków modyfikujących przebieg choroby. Postępy jakie ostatnio poczyniono w zrozumieniu patogenezy SSc przyczyniły się do wprowadzenia nowych metod leczenia. Wyniki wstępnych badań klinicznych wskazują, że mykofenolat mofetylu, przeciwciała przeciwko CD20 i przeszczepy komórek macierzystych mogą mieć korzystny wpływ w leczeniu SSc. Wieloośrodkowe badania kohortowe dostarczają cennych informacji dotyczących naturalnego przebiegu choroby co z kolei przyczynia się do poprawy opieki nad chorymi na SSc. Do najważniejszych celów tych badań należy opracowanie programów przesiewowych mających na celu wczesną diagnostykę i, w konsekwencji, wdrożenie właściwego postępowania terapeutycznego powikłań narządowych SSc, a także opracowanie zaleceń terapeutycznych.

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