Review - CME

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New insights into the pathogenesis and management of juvenile systemic sclerosis

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Systemic sclerosis remains one of the most clinically challenging diseases for rheumatologists and patients continue to suffer from a considerable degree of morbidity and mortality. Even though the pathogenesis of the disease remains complex and poorly understood, new research over the past several years have brought us closer to an understanding of the underlying disease mechanisms and complications (e.g., fibrosis, immunological abnormalities, vasculopathy). Emerging clinical data suggest that juvenile Systemic Sclerosis (jSSc) differs from systemic sclerosis in adults in both its presentation and clinical course. This review summarizes recent developments in the understanding of the immune pathogenesis and new therapeutic options for the treatment of jSSc.

Keywords: biologics • bone marrow transplantation • Campath-1H • effector memory RA (EMRA) CD4 T lymphocytes • immune pathogenesis • juvenile systemic sclerosis (jSSc) • regulatory T lymphocytes (Treg)

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LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Differentiate adult systemic sclerosis from jSSc
- Assess the pathophysiology of jSSc
- Evaluate the use of disease-modifying antirheumatic drugs for jSSc
- Analyze the efficacy and safety of autologous human stem cell transplantation for jSSc

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Scleroderma is a family of diseases with different clinical phenotypes that either manifests as localized or as systemic disease. Scleroderma is the third most common rheumatic condition in childhood after juvenile idiopathic arthritis and childhood onset systemic lupus erythematosus. Although rare in children, juvenile Systemic Sclerosis (jSSc) represents one of the most clinically challenging diseases for pediatric rheumatologists. This review will focus on new insights into the pathogenesis and the clinical management of jSSc.

Classification

JSSc is a rare childhood disorder and its incidence and prevalence remains difficult to determine. Some statistics quote an incidence ratio of around 0.3 in a million children per year and approximately 5–10% of all systemic sclerosis (SSc) cases develop before the age of 16 [1–3]. The usual childhood onset occurs around 8 years of age [4,5]. JSSc is observed with equal frequency in boys and girls before the age of 8 years, whereas girls outnumber boys 3:1 thereafter [6].

SSc in adults distinguishes two subforms: diffuse cutaneous sclerosis (dSSc) and limited cutaneous sclerosis (lSSc). Per the adult classification criteria, dSSc is characterized by diffuse sclerodermatous skin changes combined with internal organs involvement including the intestinal tract (mainly the esophagus), heart, lungs, kidneys and joints. Conversely, limited cutaneous scleroderma (lSSc) is characterized by the association of Raynaud's phenomenon with skin fibrosis limited to the hands, face, feet and forearms and mainly esophageal involvement [7].

However, emerging clinical data suggest that jSSc differs from systemic sclerosis in adults in both its presentation and clinical course. For example, lSSc is considered more rare in children but at the same time might be underrecognized in younger children since the clinical features at this age group may still be incomplete. When compared with adults, children more often present with sclerodermatous features as part of overlap syndromes. Gastrointestinal involvement is significantly less common than in adults while there is a higher prevalence of arthritis and myositis, which are often features of early disease. Similarly, interstitial lung disease, gastroesophageal dysmotility and renal involvement with arterial hypertension are much less common than in adults [8–10].

Finally, two distinct jSSc disease trajectories have been described including a more rapid progressive and fatal disease course mainly with cardiac involvement and a more 'benign' and chronic disease course with predominant pulmonary and gastrointestinal involvement [11].

In 2007 a committee on classification criteria for jSSc, that included members of the Pediatric Rheumatology European Society (PRES), the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), proposed a new classification system for systemic sclerosis in children under the age of 16 to standardize clinical and epidemiological research and assess treatment outcome [3]. Applying established consensus formation methodologies and combining clinical and laboratory features specific for the pediatric population these new classification criteria require the presence of proximal skin sclerosis/induration as major criteria, and at least 2 of 20 minor criteria as outlined in Box 1. These criteria, even though not validated, were found to have a sensitivity of 90% and a specificity of 96% and were developed to ensure a more accurate diagnosis for jSSc. They are ultimately supposed to replace the adult criteria that have been previously used in pediatric studies (Box 1).

Update on the immune pathogenesis of jSSc

The pathologic hallmark of systemic sclerosis, as the term implies, is the progressive fibrosis of the skin and internal organs especially the lungs and the gastrointestinal tract. Although the pathophysiology of systemic sclerosis (SSc) remains unknown, recent evidence suggests that auto aggressive T lymphocytes, including abnormal regulatory T lymphocytes (Treg) are cross-reacting with autologous antigens and are responsible for the initiation and maintenance of the disease [12–14]. These cells potentially react with autoantigens such as topoisomerase (TOPO) and cause damage to

vascular endothelium, with subsequent proliferation of fibroblasts and production of collagen [15,16].

Tissue biopsies of SSc patients with early disease have demonstrated mononuclear inflammatory cell infiltrates, including T-lymphocytes and macrophages near blood vessels, nerve fibers and dermal appendages indicating that an inflammatory cell infiltrate is present prior to tissue fibrosis and that homing of cytokine-producing cells may precede the accumulation of collagen [17]. In patients with nonsystemic, localized scleroderma a lack of CD34+ dendritic cells and an increase of dermal dendrocytes in areas of fibrosis have been described suggesting that they may contribute to the local fibrotic process [18]. In systemic disease, increased local cytokine production, including transforming growth factor beta (TGF-b) and connective tissue growth factor (CTGF), in addition to circulating autoantibodies lead to fibroblast activation and collagen production further supporting the concept that an altered cellular immunity plays a role in the pathogenesis of the disease. Interestingly, and as mentioned above, the tissue distribution of clinical fibrosis appears to differ between jSSc and adult SSc patients [17,19–21]. Besides the cellular and humoral aspects, SSc also has significant similarities to chronic Graft versus Host Disease (cGVHD) [22,23].

We recently studied immunological abnormalities in a population of jSSc patients followed at the Pediatric Rheumatology Core at Children's Hospital Los Angeles. Similar to reports in adult SSc patients, we hypothesized that jSSc patients have abnormalities in the numbers of their regulatory T lymphocytes (Treg) enabling the clonal expansion of autoreactive CD4 T lymphocytes that migrate to sites of inflammation and activate fibroblasts resulting in increased collagen deposition [24]. However, studies in adult SSc patients have reported conflicting results in regards to Treg lymphocytes with some investigators reporting decreases in Treg lymphocytes while others found increases in this cell population [25,26]. These

Box 1. Provisional criteria for the classification of juvenile systemic sclerosis.

Major criterion (required)
- Proximal skin sclerosis/induration of the skin

Minor criteria (at least two required)
- Cutaneous
  - Sclerodactyly
- Peripheral vascular
  - Raynaud's phenomenon
  - Nailfold capillary abnormalities
  - Digital tip ulcers
- Gastrointestinal
  - Dysphagia
  - Gastroesophageal reflux
- Cardiac
  - Arrhythmias
  - Heart failure
- Renal
  - Renal crisis
  - New-onset arterial hypertension
- Respiratory
  - Pulmonary fibrosis (HRCT/radiography)
  - Decreased DLCO
  - Pulmonary arterial hypertension
- Neurologic
  - Neuropathy
  - Carpal tunnel syndrome
- Musculoskeletal
  - Tendon friction rubs
  - Arthritis
  - Myositis
- Serologic
  - Antinuclear antibodies
  - SSc-selective autoantibodies (anticentromere, anti–topoisomerase I [Scl-70], antifibrillarin, anti–PolyMyositis-Scleroderma (PM-Scl), antifibrillin or anti–RNA polymerase I or III)

DLCO: Diffusing capacity for carbon monoxide; HRCT: High-resolution computed tomography; SS: Systemic sclerosis.

conflicting results may be based on the differences in criteria used to identify Treg lymphocytes, which traditionally included the expression of FoxP3 and/or CD25. These criteria, however, are confounded by the fact that activated conventional T lymphocytes (aTcon) express both FoxP3 and CD25 [27,28]. In contrast to mice, however, in which all functional Treg lymphocytes express FoxP3, not all FoxP3 expressing human Treg lymphocytes are functional [29].

For the studies in our jSSc population and in order to get a more accurate assessment and quantification of the functional Treg lymphocytes, we used the Miyara classification that differentiates aTcon lymphocytes from both resting regulatory T lymphocytes (rTreg) and activated regulatory T lymphocytes (aTreg) [30]. In normal individuals rTreg lymphocytes usually represent 20% of the total Treg lymphocytes while aTreg lymphocytes represent 5%. Thus, in humans, only 25% of the total Treg lymphocytes (CD4+, CD127-, CD25+) have regulatory function. The remaining FoxP3 expressing Treg lymphocytes (50% of the total Treg lymphocytes) are aTcon lymphocytes based on their functional characteristics [cytokine production (γ-interferon, IL-2, IL-17) and a proliferative response to allogeneic lymphocytes [29].

Of the ten patients in our cohort nine had significantly decreased rTreg lymphocytes when compared with a control population. While the total frequency of all FoxP3 expressing T lymphocytes was the same in both groups, the jSSc patients had significant decreases in their aTreg lymphocytes due to the increased frequency of aTcon lymphocytes (Figure 1). These results are similar to recently published data in patients with active chronic cGVHD and may explain the conflicting results from studies in adult SSc patients, where an increase in aTcon lymphocytes may have been misinterpreted as increases in Treg lymphocytes [31].

In order to evaluate whether the decrease in the frequency of rTreg in the jSSc patients was due to a decreased production of new rTreg or an increased conversion to Th17 cells, we assessed the thymic contribution to the rTreg lymphocyte population, by determining the frequency of recent thymic emigrants (RTE) in the rTreg subpopulation. We found no difference in the RTE content of rTreg in jSSc patients when compared with normal individuals, which suggests that the decrease in rTreg is due to their increased conversion to Th17 lymphocytes. These cells may migrate to sites of clinical disease, as recently described in animal models and contribute to the development of jSSc [32–35].

Our data were limited by the sample size and the fact that we were not able to determine if the decrease in rTreg lymphocytes was a primary event in the pathogenesis of jSSc or a secondary event as a result of either disease progression and/or affiliated therapy. However, recent published data in patients with active cGVHD suggest that the observed differences in the frequencies of both RTEs and rTregs are not related to immunosuppressive therapy, since there was neither a decrease in the frequency or number of RTEs in the treated subpopulation nor a significant difference between patients who were aggressively treated or received less aggressive maintenance therapy [31]. Longitudinal studies of newly diagnosed jSSc patients will have to determine if there are alterations in the frequency of rTreg lymphocytes in jSSc patients from the time of their initial diagnosis, which may be challenging since many patients are not diagnosed in a timely manner [36]. Lastly the low concordance rate of jSSc in identical twins seems to suggest that the clonal expansion in these cells represents an epigenetic phenomenon [37].

Another unexpected finding in our jSSc population was the marked increase in the frequency of the effector memory RA (EMRA) CD4 T lymphocyte subpopulation, which has been reported in patients with chronic viral infections, other autoimmune diseases and normal elderly individuals but not in SSc patients [38–40]. However, unlike in these other populations where the EMRA T lymphocytes were characterized by a loss of CD28 expression and the acquisition of NKG2D expression, we found neither in our jSSc patients, suggesting that the increased EMRA CD4 T lymphocyte subpopulation present in the jSSc patients differs from that found in other diseases (Figure 2).

While prior studies have identified clonal CD4 T lymphocytes in both the peripheral blood and skin of adult SSc patients, the immunophenotype of the clonal T lymphocytes has not been determined [16,21,41]. Moreover, until the publication of our data, no clonal studies had been conducted in jSSc patients. Previous studies on autoreactive T lymphocytes in adult SSc patients had identified the increased usage of distal VJ segments specific for topoisomerase [42]. In our study cohort we were able to demonstrate a significant increase in the TCR usage of distal VJ segments (J2–1 to J2–7) while we were not able to detect an increase in TCR Vb clonality of whole memory CD4 T lymphocytes from jSSc patients [K Weinberg; Unpublished Data].

This suggests that the expanded EMRA T lymphocyte subpopulation may include the clonally expanded CD4 T lymphocytes and further identification of clonal CD4 T lymphocytes involved in the pathogenesis of systemic sclerosis in children and adolescents could utilize the measurement of increased distal VJ segment usage in these EMRA CD4 T lymphocytes. We are currently directing our research towards the

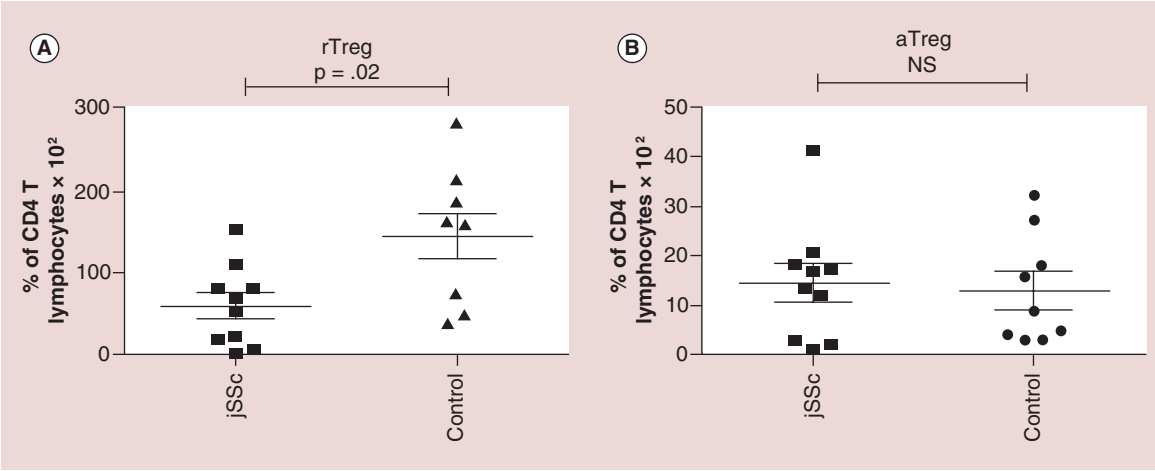

Figure 1. Frequency of Treg lymphocyte subpopulations in juvenile systemic sclerosis patients and control individuals. (A) Resting Treg lymphocytes (rTreg; $CD4^+$, $CD127^-$, $CD25^+$, $CD45RA^+$, $FoxP3^+$) and **(B)** activated Treg lymphocytes (aTreg; $CD4^+$, $CD127^-$, $CD25^+$, $CD45RA^-$, $FoxP3^{+++}$). Frequencies are presented as a percentage of total CD4 T lymphocytes (% rTreg/aTreg × % Treg population).
aTreg: Activated Treg lymphocytes; jSSC: Juvenile Systemic Sclerosis; NS: Not Significant; rTreg: Resting Treg lymphocytes.

clonal analysis of the EMRA T lymphocyte subpopulation using high throughput TCR sequencing (HTS) [43].

We also examined the potential role of chemokines and chemokine receptors in the tissue -specific migration of T lymphocytes in our jSSc population, by performing leukocyte exon gene array analyses. Chemokine receptors such as CCR7 are of particular interest in scleroderma since they control the migration of peripheral blood T lymphocytes to peripheral lymph nodes and play a role in the tissue -specific distribution of fibrosis [44]. Recent reports have established that CCR7 expression by dermal fibroblasts functions as a receptor for topoisomerase resulting in the activation of the fibroblasts [15]. On the other hand CCR7 expression is certainly not specific for scleroderma since it is also expressed on 80% of T lymphocytes present in normal skin, and involved in the skin tropism of patients with Sezary Syndrome and psoriasis [45,46].

We were able to detect an increased expression of ubiquiten B, GRAP, CCR7 and CD22 in our jSSc population which was partly consistent with previous reports in adult SSc patients that found an increased expression of CD22 on B-lymphocytes [47], but the increased expression of ubiquiten B, GRAP, CCR7 has never been reported in children or adults with SSc before.

To confirm the increased RNA expression of CCR7 at the protein level, we determined the surface expression of CCR7 on the CD4 T lymphocytes subpopulations. Consistent with our exon array data we found an increased frequency of CCR7 expressing cells in all CD4 T lymphocyte subpopulations although the magnitude of CCR7 expression was not statistically significant for the naive subpopulation. Thus, CCR7 may play a role in the cutaneous migration of CD4 T lymphocytes, their activation and contribution to the tissue-specific distribution of clinical fibrosis.

Even though the impact of this observation is not yet entirely understood, we believe that the expression of these chemokines and chemokine receptors signify the result of chronic antigenic stimulation as previously reported by others during chronic viral infection [44].

Similar to our observations with the decrease in rTreg lymphocytes, we were not able to establish whether the increased frequency of CCR7 expressing cells would represent a finding at the time of initial diagnosis or was a secondary effect of disease progression or treatment.

Update on the treatment of jSSc

Even though recent data reaffirmed that the overall prognosis of childhood systemic sclerosis is more favorable than in adults, patients suffer from a considerable degree of morbidity. When severely affected, children tend to have a more rapid disease progression as compared to adults [2,5]. Excluding pulmonary arterial hypertension, cardiac death is the most common cause of mortality in children with jSSc and occurs in 25% to over 50% of all patients. Hence, there is a critical need for effective therapies to treat this devastating disease [48].

While there may be a role for traditional disease modifying antirheumatic drugs (DMARDs) such as methotrexate in the treatment of localized scleroderma, there are currently no effective treatments for children with jSSc. In adults and children cyclophosphamide

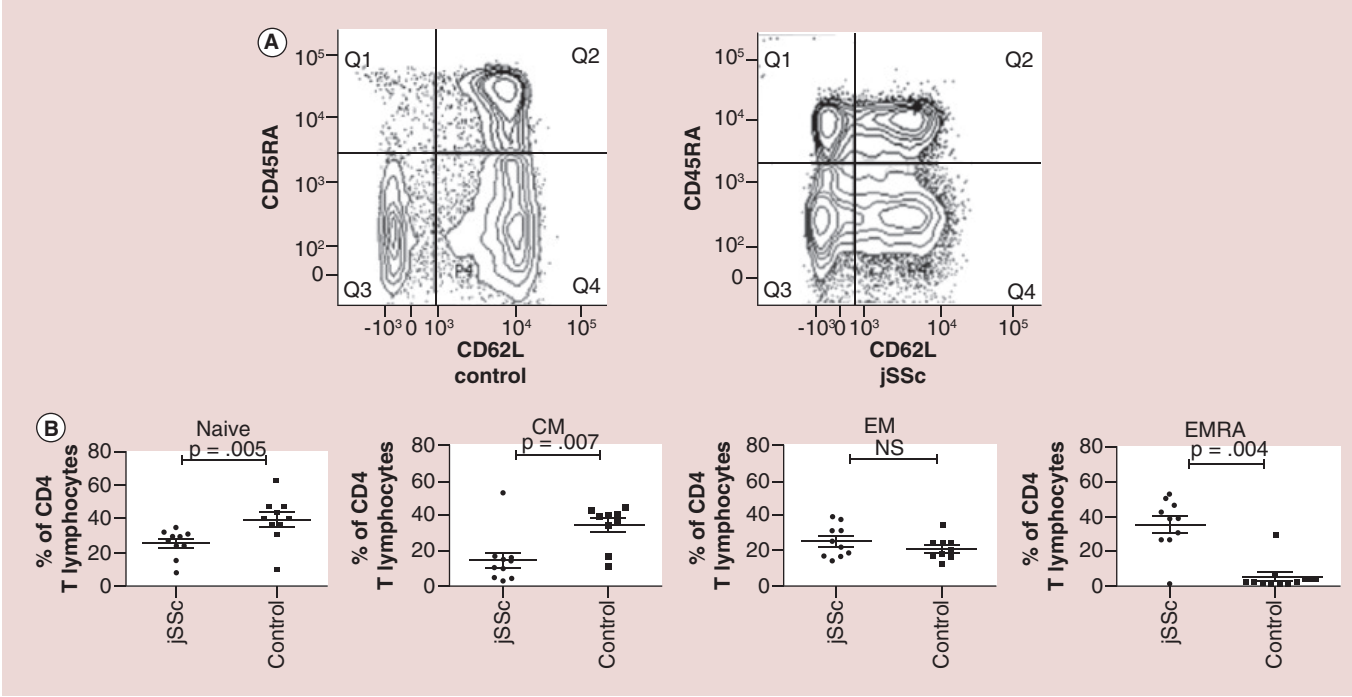

Figure 2. Frequency of CD4 T lymphocyte subpopulations from juvenile Systemic Sclerosis patients and control individuals.
(A) Identification of CD4 T lymphocyte subpopulations in a control individual and a jSSc patient: Q1 = CD45RA expressing effector memory (EMRA: $CD45RA^+$, $CD62L^-$); Q2 = naive ($CD45RA^+$, $CD62L^+$); Q3 = effector memory (EM; $CD45RA^-$, $CD62L^-$); and Q4 = central memory (CM; $CD45RA^-$, $CD62L^+$). **(B)** Naive, CM, EM and EMRA. Frequencies are presented as a percentage of total CD4 T lymphocytes.
CM: Central memory; EM: Effector memory; EMRA: Effector memory CD45RA-expressing CD4 lymphocytes; jSSC: Juvenile Systemic Sclerosis.

is often used as induction therapy for lung and severe skin disease while mycophenolate, azathioprine and methotrexate are used for maintenance therapy or for patients with scleroderma overlap syndrome. However to date, none of the limited number of randomized, controlled clinical trials with these DMARDs in adult or childhood systemic sclerosis have been able to demonstrate a therapeutic effect in either preventing disease progression or reversing fibrosis [49–58]. As a result of these discouraging findings, therapy in SSc remains largely organ-specific encompassing endothelin receptor antagonists, phospho-diesterase inhibitors or prostanoids for pulmonary arterial hypertension and angiotensin-converting enzyme inhibitors (ACEi) for renal disease [59–63].

Biologics in the treatment of systemic sclerosis

Unlike in other rheumatologic diseases, clinical trials using first and second-generation biologic drugs have so far failed to show any major therapeutic benefit for patients with systemic sclerosis. Most of the published studies consist of smaller case series and none of them were exclusively pediatric. The earlier studies investigated tumor necrosis factor inhibitors (TNFi) such as infliximab with limited to no success on skin scores, laboratory markers of collagen synthesis or pulmonary fibrosis, while they may have had a beneficial effect on disability scores in patients with SSc associated arthritis [64,65]. In the more recent studies with second-generation biologics including Rituximab (RTX), tocilizumab and abatacept, RTX initially appeared to show potential efficacy in improving skin fibrosis and preventing worsening lung fibrosis, especially when used in patients with early disease. Two more recent studies with tocilizumab and abatacept demonstrated little to no effect for any change in fibrotic lesions [66–70]. Our personal anecdotal experience of treating two children with tocilizumab has been rather positive, yet lack of long-term data currently limits our assessment. In a recently published systematic literature review of biologics for the treatment of systemic sclerosis using published evidence from Medline, Embase, CINAHL and the Cochrane Database evaluating 23 studies including 3 on infliximab, 3 on etanercept, 3 on antithymocyte globulin, 3 on imatinib, 6 on rituximab and 1 study each on interferon-γ (IFN-γ), IFN-α, relaxin, deglycolipidated Mycobacterium vaccae, human antitransforming growth factor ß1 antibody, and oral type I collagen, none of the reviewed drugs showed any reproducible, statistically significant benefit on the underlying fibrotic process in the skin or the internal organs [71].

The role of bone marrow transplantation in the treatment of systemic sclerosis

As a treatment often still considered as last resort, autologous Human Stem Cell Transplantation (aHSCT) has been studied in both adult and pediatric patients with refractory rheumatologic diseases including systemic sclerosis [72–80]. The hypothesis behind this therapeutic approach is the resetting of the aberrant immune response through either hematopoietic stem cell replacement or through immunomodulation with mesenchymal stem cells. Among all rheumatologic diseases, refractory systemic sclerosis (SSc) and systemic lupus erythematosus (SLE) have been the most common indications for aHSCT. Clinical benefits have been reported in approximately 30% of patients in all disease categories. By 2011, 175 adult and pediatric patients had received predominantly autologous HSCT for systemic sclerosis [81,82]. The proposed hypothesis for the therapeutic benefits of HSCT in systemic sclerosis in particular is based on the elimination of the effector mechanisms that produce the inflammatory response and the subsequent increased collagen deposition. In fact, a recent study demonstrated that the decreased frequency and the functional defect of peripheral Treg cells from adult patients with dSSc autocorrected following aHSCT and approached levels measured in healthy controls [83].

However, sufficient thymic reconstitution of peripheral T lymphocytes after HSCT is a critical component of immune recovery in order to avoid a chronically immunodeficient state or the risk of disease recurrence and an important consideration that appears to be frequently forgotten prior to HSCT. As a result we assessed the thymic function of 13 children and adolescents with treatment refractory SSc, awaiting aHSCT by including a physical exam, a MRI of the chest, as well as functional immune studies including B and T cell immunophenotyping, measurement of autoantibodies and quantization of T cell receptor rearrangement excision circles (TREC) as a marker of thymopoiesis [84]. We found that MRI detected thymic tissue in only 9/13 children. Moreover, even though we were able to detect TREC levels in all but one child, they were significantly reduced ($p < 0.001$) when compared to a control population. In addition, jSSc patients had a reduced percentage of naive (CD45RA+CD31+) CD4+ T lymphocytes suggestive of a diminished thymopoesis with potential for an inadequate immune-reconstitution following transplantation in some patients. As a result of our study we recommended that careful screening for adequate thymopoesis should be initiated prior to transplantation in all patients with jSSc and those patients with absent thymic tissue and a thymic function of less than 5% RTE of a normal lymphocyte count should not be considered for immunoablative therapy.

Initial uncontrolled trials with aHSCT demonstrated that approximately 70% of the transplanted patients experienced significant improvements in their skin scores and some a trend toward stabilization in their lung function. Nevertheless, disease progression occurred in almost 20% of patients and the procedure-related mortality rate was high ranging from 10 to 20% [72].

At the time of this manuscript there were five reported pediatric patients (four female/one male) with jSSc (four with dSSc and one with lSSc) under the age of 18 years (median age at the time of HSCT 12 years [range 9–17]) that had been treated with aHSCT. The average disease duration prior to aHSCT was 5 years (range 2–7 years) and all patients had established lung disease. Conditioning treatments consisted of cyclophosphamide with anti-CD52 (CAMPATH 1) (n = 3), cyclophosphamide with TBI and ATG (n = 1), or cyclophosphamide alone (n = 1). After a median follow up of about 3 years (range 1–5.5 years) three patients had achieved complete remission with improvement in growth rate, skin softening and general well-being. One patient achieved partial remission, and one patient relapsed 9 months after initially achieving remission. High-resolution pulmonary CT (HRCT) scans did not show any progression of the interstitial fibrosis in the first three children, but detected further progression in the fifth child that had experienced a disease relapse [75,76]. Engraftment of neutrophil and platelet function usually occurred within 2 weeks while a complete immunologic reconstitution usually required 7 months [85,86].

In summary, these early Phase II trials with aHSCT demonstrated that this therapeutic intervention produced impressive initial clinical results that had not been previously seen with any other treatments. However, lower mortality and durability of the clinical response strongly hinged on the appropriate patient selection, especially those with early and less advanced disease.

Following these initial uncontrolled trials, several new controlled studies comparing autologous HSCT to immune-suppression mainly in adult patients with SSc are presently being conducted in both the United States and Europe with the principal difference that European trials only use chemotherapy while US trials employed both chemotherapy and total body irradiation (TBI) [87,88]. Most of these studies including the larger *Scleroderma: Cyclophosphamide or Transplantation (SCOT)* trial (ClinicalTrials.gov Identifier: NCT00114530) are still awaiting final data evaluation and publication.

Future perspective

Due to the variability in the clinical response and the high treatment mortality rate of HSCT, new treatment alternatives have been sought in order to avoid the risks associated with the chemotherapy and radiation used in the transplantation protocols. Several newer biologic agents such as belilumab, a human monoclonal antibody that inhibits B-cell activating factor (BAFF), and antagonists selective for the lysophosphatidic acid receptor (LPA-1) that among others mediates vascular leakage and myofibroblast recruitment are currently being studied in either preclinical animal models or early phase human trials for fibrosis associated with SSc. In addition, small molecule inhibitors including tyrosine kinase inhibitors, JAK-2 inhibitors, inhibitors of CCN2 (formerly known as connective tissue growth factor) considered a central mediator of fibrosis, anti-IL-13 antibodies, thrombin antagonists or bortezomib, a small molecule proteasome inhibitor with antifibrotic properties, have shown some promise *in vitro* and animal studies of fibrosis and some are being studied in early clinical human trials. An excellent summary of these emerging therapies has recently been published [89].

Another promising agent is Campath-1H, the humanized version of a murine monoclonal antibody to human CD52, which recognizes and specifically binds to CD52, a small glycoprotein expressed on the surface of essentially all normal and malignant T and B cells, a majority of monocytes, macrophages and natural killer (NK) cells but not on erythrocytes or hematopoietic stem cells [90]. For many years Campath has been used as an immunosuppressive agent in solid organ transplantation, as part of the preparative regimes for allogeneic HSCT including SSc, successfully preventing graft-versus-host-disease (GVHD) and as treatment for patients with various autoimmune diseases who were nonresponsive to standard immunosuppressive agents [91–95]. In the United States, Campath-1H is FDA approved for the treatment of CLL but is also in general use as an immunosuppressive agent in HSCT. This drug may be of particular importance in SSc since a majority of infiltrating T-cells in scleroderma skin lesions expresses activation markers such as CD52, which is the target of Campath therapy [96–99]. Although Campath has not been generally considered an immunoablative agent for any autoimmune disease, we published a case of successful immunoablation using high dose Campath in a patient with an 11-year history of severe progressive, treatment refractory polymyositis [100]. Our results suggest that similar to HSCT immunoablation with high dose Campath monotherapy is possible without the associated risks of chemotherapy and radiation. As a result of this case report, we are currently studying high dose Campath as immunoablative therapy for children and adolescent with early treatment refractory SSc.

Finally another potential appealing therapeutic approach for treatment resistant SSc may be borrowed from the experience of treating cGVHD with low-dose interleukin-2 [101]. As outlined above there are significant similarities between cGVHD and SSc. The hypothesis behind this approach is the *in vivo* stimulation and proliferation of Treg cells with the therapeutic goal to suppress the clinical manifestations of SSc. In a recent study, 29 adult patients with active chronic steroid refractory cGVHD were treated with daily low-dose subcutaneous interleukin-2 (0.3 × 106, 1 × 106, or 3 × 106 IU per square meter of body-surface area) for 8 weeks. Subsequently numbers of CD4+ Treg cells increased more than eight times from baseline in all patients, with a peak at 4 weeks, while Tcon remained unaffected. Treg cell counts and Treg:Tcon ratios remained elevated for about 8 weeks but then declined when patients were no longer receiving interleukin-2. Treatment with interleukin-2 allowed for the reduction of concomitant steroids by a mean of 60% (range 25–100%). While none of the patients had a relapse or progression of their cGVHD, two patients developed thrombotic microangiopathy–associated renal failure requiring dialysis, three had serious infections, one patient each had lower gastrointestinal bleeding and Grade 3 deep-vein thrombosis with left ventricular thrombus and two patients experienced an MI one of which was fatal. Considering our published data as described above this treatment may become a viable option for children and adolescents with jSSc, potentially correcting our observed decrease in the frequency of both resting and activated Treg lymphocytes.

Conclusion

The past several years have brought us closer to an understanding of the pathogenesis of systemic sclerosis and new therapies directed at controlling the underlying disease process and its complications (e.g., fibrosis, immunological abnormalities, vasculopathy) are in the development. After many years of failed therapies, the treatment of dSSc in children and adults currently remains symptomatic and organ focused. The EULAR Scleroderma Trials and Research (EUSTAR) group has established a group of evidence-based recommendations to be used in clinical practice with the main aim to provide guidance for adult and pediatric rheumatologists to correctly approach and choose the treatment for SSc patients [102]. Yet based on a critical review of currently published data, an early aggressive approach including HSCT appears to be the most effective way to reduce long-term morbid-

ity and mortality. Future therapeutic concepts have to consider that early aggressive immunoablative therapy with high short-term risk may be more efficacious for the induction of disease remission than long-term, lower risk DMARD or biologic therapy. Based on research from others and us, targeted therapies towards resetting the ratio of resting and activated T regulatory cells might become an appealing concept for future therapies away from the current organ-specific approach (Box 1).

Executive summary

- Juvenile systemic sclerosis (jSSc) differs from systemic sclerosis in adults in both its presentation and clinical course, and children more often present with sclerodermatous features as part of overlap syndromes. As such there is a higher prevalence of arthritis and myositis while interstitial lung disease, gastroesophageal and renal involvement are less common than in adults. A new systemic sclerosis classification system specifically for children has been proposed by a collaboration of the Pediatric Rheumatology European Society (PRES), the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR).
- Immunological evaluations have shed new light on the pathogenesis of this disease in children and adolescents with established jSSc. Similar to other autoimmune diseases these patients have reduced numbers of both resting and activated Treg lymphocytes, an increased frequency of EMRA CD4 T lymphocytes, and an increased expression of CCR7 by CD4 T lymphocyte subpopulations. It remains to be seen whether similar abnormalities can be found in adult SSc patients, and whether these immune abnormalities are present at the time of initial clinical presentation, or are related to chronic disease and affiliated immunosuppression.
- Even though the overall prognosis of childhood systemic sclerosis is more favorable than in adults, children suffer from a considerable degree of morbidity. While traditional DMARDs might be helpful for myositis and arthritis associated with scleroderma, they are generally ineffective for children with jSSc. Endothelin receptor antagonists, phospho-diesterase inhibitors, prostanoids and angiotensin-converting enzyme inhibitors have significantly improved the prognosis and quality of life for patients with pulmonary arterial hypertension and renal disease. The newer first and second-generation biologic drugs have so far failed to show any major therapeutic benefit for patients with systemic sclerosis. Preliminary trials with aHSCT demonstrated impressive initial clinical results that had not been previously seen with any other treatments and patients with early and less advanced disease had the best outcome. Many new promising therapies for this devastating disease are currently being evaluated in early clinical trials.

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•• **Excellent summary and guidance for treatment recommendations in SSc.**

New insights into the pathogenesis and management of juvenile systemic sclerosis

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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.	1	2	3	4	5
The activity supported the learning objectives.					
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The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

1. You are seeing an 8-year-old boy recently diagnosed with jSSc. His parents have read online about systemic sclerosis in general and are concerned with their son's risk for morbidity. Which one of the following body systems tends to be more affected by systemic sclerosis among children vs adults?
   - ☐ **A** Gastrointestinal
   - ☐ **B** Muscle and joint
   - ☐ **C** Renal
   - ☐ **D** Pulmonary

2. Which one of the following should you consider regarding immune system changes associated with jSSc as you evaluate this child?
   - ☐ **A** jSSc is associated with higher levels of activated regulatory T (Treg) lymphocytes only
   - ☐ **B** jSSc is associated with higher levels of resting and activated Treg lymphocytes
   - ☐ **C** jSSc is associated with an increased frequency of effector memory rheumatoid arthritis CD4 T lymphocytes
   - ☐ **D** Chemokine receptors such as CCR7 do not appear related to the pathogenesis of jSSc

3. Which one of the following should you consider regarding pharmacologic treatment options for jSSc as you treat this patient?

- ☐ **A** All children should receive a trial of methotrexate
- ☐ **B** Treatment with infliximab usually results in markedly improved skin scores and reduced pulmonary fibrosis
- ☐ **C** Tocilizumab and abatacept are now considered the standard of care
- ☐ **D** DMARDs are generally ineffective for jSSc

4. You also consider autologous human stem cell transplantation (aHSCT) for this patient. Which one of the following statements regarding aHSCT in the treatment of jSSc is most accurate?

- ☐ **A** aHSCT has been demonstrated to reduce peripheral Treg lymphocyte activity among adults
- ☐ **B** Small studies confirm that thymic reserve is not an issue before aHSCT for children with jSSc
- ☐ **C** aHSCT can improve skin lesion scores and stabilize pulmonary function
- ☐ **D** aHSCT has not led to remission from jSSc