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Immunotherapy of systemic sclerosis

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Abstract

Scleroderma is a multisystem autoimmune disease characterized by an abnormal immune activation associated with the development of underlying vascular and fibrotic disease manifestations. This article highlights the current use of drugs targeting the immune system in scleroderma. Nonselective immunosuppression, and in particular cyclophosphamide, remains the main treatment for progressing skin involvement and active interstitial lung disease. Mycophenolate mofetil is a promising alternative to cyclophosphamide. The use of cyclosporine has been limited by modest efficacy and serious renal toxicity. Newer T-cell (sirolimus and alefacept) and B-cell (rituximab)-targeted therapies have provided some encouraging results in small pilot studies. Hematopoietic stem cell transplantation can be effective for severe fibrotic skin disease, but toxicity remains a concern. Clinical efficacy and safety of antifibrotic treatments (e.g., imatinib) await confirmation. Newer biological agents targeting key molecular or cellular effectors in scleroderma pathogenesis are now available for clinical testing.

Keywords

immunotherapy; scleroderma; systemic sclerosis; treatment

Scleroderma or systemic sclerosis (SSc) is a rare multisystem autoimmune disease characterized by immune abnormalities, fibrosis of the skin and internal organs, and obliterative vasculopathy predominantly affecting the microvascular circulation [1]. Skin fibrosis is the dominant feature of the disease and can be confined distally to the knees or elbows in the limited SSc subset (lcSSc) or involve the proximal portion of the extremities as well as the trunk in the diffuse form (dcSSc) [2].

Internal organ involvement represents the most important determinant of morbidity and mortality in SSc. In particular, pulmonary fibrosis and pulmonary hypertension are responsible for the majority of SSc-related deaths [3]. Median survival in SSc patients with pulmonary hypertension ranges between 1 and 3 years [4]. In subjects with severe progressive pulmonary fibrosis the mean survival is less than 3 years [5]. The pathogenetic mechanisms involved in SSc are tightly intertwined throughout the disease process, but the degree of their contribution varies over time. An abnormal immune activation involving humoral as well as cellular events appears to be a fundamental step for disease initiation.

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The presence of SSc-specific autoantibodies is preferentially associated with particular disease manifestations (i.e., antitopoisomerase-1 or Scl-70 with diffuse skin and interstitial lung involvement) and titers broadly correlate with disease activity and severity [6,7]. Sequential skin biopsies obtained from SSc lesions during early phases of the disease have demonstrated that a perivascular mononuclear infiltrate, predominantly composed of $CD4^+$ and $CD8^+$ T cells, precedes the development of fibrosis [8]. Likewise, pathologic studies on SSc patients with early lung involvement have confirmed that an intense interstitial and alveolar inflammatory infiltrate is present before the development of pulmonary fibrosis [9]. T lymphocytes in particular appear to have a central role in this process and are required for initiation and propagation of the fibrotic lung insult. In mice, Bleomycin-induced pulmonary fibrosis is inhibited by T-cell depletion strategies and T-cell-deficient animals (athymic nude mice) do not develop the disease [10–12]. In SSc patients with active alveolitis, $CD8^+$ T cells with an activated phenotype human leukocyte antigen-DR ($HLA\text{-}DR^+$) predominate and correlate with more severe pulmonary fibrosis [13].

Experimental data also support the evidence that early events leading to SSc vasculopathy, such as endothelial cell dysfunction and injury, are at least in part mediated by an immune activation [14]. The presence of antiendothelial cell antibodies in SSc sera and their involvement in antibody-dependent cell cytotoxicity of the endothelium have been widely reported [15]. In addition, endothelial cell apoptosis has been linked to the release of granule content and granzymes from cytotoxic T cells, and to the direct interaction with other cytolytic effectors (i.e., γδ lymphocytes) [16].

Importantly, while the inflammatory events become less intense or even subclinical during later stages of the disease process, the immune response retains the ability to function as a low-grade amplifier of fibrogenesis and microangiopathy in virtue of its peculiar functional properties. In particular, experimental data suggest that a network of profibrotic cellular and humoral mediators is established in SSc patients, particularly within target tissues (e.g., skin and lung). Cytokines, such as IL-4 and IL-13, are elevated in the blood of SSc patients [17,18]. IL-4 expression and secretion is increased in T cells from newly affected skin [19,20]. Activated $CD8^+$ T cells in the bronchoalveolar lavage fluid of SSc patients with alveolitis have higher type 2 cytokine (IL-4 and -5) mRNA expression; this predicts the subsequent decline of respiratory function [21]. This Th2/Tc2 polarized microenvironment can promote and perpetuate fibroblast activation, proliferation and differentiation into myofibroblasts, leading to tissue fibrosis and, at the vascular level, to intimal hyperplasia and vessel obliteration. TGF-β plays a central role in this process. Immune effectors can upregulate TGF-β function by increasing its expression, stimulating its secretion and regulating its activation from the latent form.

Intriguingly, the presence of potentially ‘pathogenic’ antibodies with the ability to promote specific pathways leading to fibrosis has recently been identified in SSc patients [22]. Antifibrillin-1 antibodies, identified in 34–80% of cases, can activate fibroblasts and induce profibrotic functions through TGF-β-mediated mechanisms [23]. It is plausible that these autoantibodies interfere with the stabilization of latent TGFβ in the extracellular matrix exerted by fibrillin-1. Antibodies directed to the PDGF receptor with agonistic function have also been detected in SSc sera [24].

The complex and pleiotropic nature of the immune response in SSc constitutes a great therapeutic challenge. Nonselective immunosuppressive treatments, which are commonly employed during early phases of SSc to control skin and lung inflammation, tend to lose their efficacy once the disease process enters a chronic phase. Furthermore, they have not demonstrated the ability to impact the progression of SSc vasculopathy. In addition, these medications are often titrated based exclusively on the crude clinical response or avoidance

of adverse effects and carry significant morbidity and mortality. For this reason, there has been a significant focus on developing novel therapies with direct antifibrotic and vasoprotective properties. Nevertheless, the close interrelationship between an abnormal immune response and the initiation and propagation of the other SSc pathogenetic events clearly supports the potential usefulness of targeting specific cellular and/or molecular immune effectors to achieve a selective 'disease-modifying' effect.

In this article, the current use of immunotherapy in SSc will be discussed (TABLE 1).

Nonselective immunotherapy

Nonselective immunosuppressive medications, primarily available for cancer chemotherapy or to prevent rejection after organ transplantation, have been used for decades to treat autoimmune disorders, including many rheumatologic conditions such as systemic lupus erythematosus and rheumatoid arthritis. General immunosuppression is usually employed in SSc to treat specific organ manifestations, such as early progressing skin disease, active interstitial lung disease (ILD), and underlying inflammatory joint or muscle disease.

Cyclophosphamide (CYC) is an alkylating agent that exerts its anti-inflammatory function through direct cytoxicity of bone marrow precursors and mature lymphocytes, leading to a consequent reduction of T and B cells as well as a prolonged decrease of the CD4:CD8 T-cell ratio [25,26]. Efficacy of CYC in SSc-related ILD has been tested in two randomized placebo-controlled trials. In the Scleroderma Lung Study (SLS), a statistically significant but modest treatment benefit was demonstrated on lung function with a 2.53% improvement of the forced vital capacity (FVC) in the group receiving daily oral CYC (1–2 mg/kg) for 1 year [27]. This benefit was sustained at 18 months but was completely lost after 2 years of follow-up, suggesting that a sequential or maintenance immunosuppressive approach may be required to retain the clinical response [28]. In addition to its effects on lung function, the SLS investigators demonstrated that the modified Rodnan's skin score (mRSS) decreased dcSSc patients treated with CYC by 3.06 points, which was significantly greater than placebo (95% CI: −3.54–−0.52) [27]. In the second study, monthly intravenous CYC followed by azathioprine (AZA) maintenance therapy demonstrated similar results with a 4.19% improvement of FVC in the treatment group compared to placebo, but only with a trend toward statistical significance ($p = 0.08$) [29]. A third randomized unblinded trial comparing daily oral CYC to AZA for 18 months also observed a trend toward improved FVC in the CYC-treated group (+3.3%) [30]. Notably, a significant decline in FVC (−11.1%) was detected among the AZA-treated patients. A meta-analysis conducted by Nannini *et al.*, including these trials and other observational studies, concluded that while an overall improvement of the pulmonary function is present in CYC-treated SSc patients, this is not clinically significant (<10% of the predicted values) [31]. Another study using an immunoablative high-dose intravenous CYC regimen without stem cell rescue demonstrated efficacy in improving skin thickening among individuals with active dcSSc [32].

Mycophenolate mofetil (MMF) is an immunosuppressant with antiproliferative effects on inflammatory cells achieved through the inhibition of the ionosine 5′-monophosphate dehydrogenase (IMPDH), an enzyme involved in the *de novo* synthesis of purines [25,33]. MMF preferentially inhibits the type-II isoform of IMPDH, which is selectively expressed on activated T and B lymphocytes preventing their proliferation and effectively suppressing antibody responses [25,33]. These properties, and the MMF favorable side-effect profile, have prompted its use in several rheumatic diseases, often as an alternative to the more toxic CYC [34,35]. In SSc, small retrospective studies have demonstrated moderate benefits from MMF with improvement of the vital capacity by 4.2% (95% CI: 1.9– 6.5%) of the predicted value per year in patients treated for 6 or more months [36] or stabilization of the FVC in

patients treated for at least 12 months [37]. In another retrospective analysis, MMF demonstrated efficacy in reducing the progression of pulmonary fibrosis (defined as a 15% reduction in FVC from baseline or a FVC of <55%) in treated versus untreated controls after 5 years of follow-up [38]. A small open-label prospective study of early dcSSc patients demonstrated improvements of carbon monoxide diffusing capacity (DLCO; +11.2% of predicted value) and FVC (+10.6%) after 4–6 months of treatment with MMF [39]. In a second open-label prospective study of 15 patients with dcSSc, MMF treatment for 12 months was associated with a significant decrease in skin score ($p < 0.001$) and an improvement of pulmonary function tests (FVC, total lung capacity [TLC] and DLCO) [40]. These positive preliminary studies have sparked great interest in further investigating the efficacy of MMF compared to CYC for the treatment of SSc-associated ILD. With this purpose, a randomized double-blind controlled trial is currently underway (SLS II).

Azathioprine inhibits the proliferation of different inflammatory cells, including T and B lymphocytes, and the formation of autoantibodies through interference with purine synthesis by its active metabolites (6-mercaptopurine and 6-thioinosinic acid) [25]. In a small retrospective study, treatment with AZA alone showed stabilization of lung function in patients with SSc-related ILD [41]. However, this beneficial effect was not confirmed in the trial by Nadashkevich *et al.* where AZA treatment did not prevent worsening of ILD as opposed to CYC [30]. Two open-label studies explored the role of AZA as a maintenance therapy in SSc following primary CYC immunosuppression [42,43]. Paone *et al.* found no deterioration in FVC, DLCO or skin score in 13 patients with early dcSSc who received AZA for 1 year following 1 year of intravenous CYC [42]. In a retrospective study, 27 SSc patients with progressive ILD treated with intravenous CYC for 6 months and maintained on AZA for 18 months demonstrated stable or improved lung function in 70 and 51.8% of patients after 6 and 24 months of follow-up, respectively [43].

Methotrexate (MTX) is an antimetabolite drug that competitively inhibits dihydrofolate reductase and leads to impaired DNA and nucleotide synthesis [25]. While MTX can result in substantial cytotoxicity (i.e., cancer therapy), its use at lower doses and supplementation with folic acid has effectively minimized side effects and has made it suitable for the treatment of inflammatory autoimmune diseases. Additional mechanisms may be involved in MTX's immunomodulatory action, such as decreased proinflammatory cytokine production, extracellular adenosine release and inhibition of antigen-induced T-cell activation [44]. MTX is frequently used in SSc to treat associated inflammatory arthritis and myositis. Its efficacy on skin disease and lung function has been investigated in two randomized placebo-controlled trials [45,46]. In the first study, patients receiving weekly intramuscular injections of MTX (15 mg) demonstrated an improvement in their mean skin scores (−0.7 mRSS; 95% CI: −3.4–2.1) compared to placebo after 24 weeks (+1.2 mRSS; 95% CI: −1.2–3.5) [45]. However, this was not statistically significant ($p = 0.06$) probably owing to the small number of patients, the inclusion of lcSSc subjects and the wide range of disease duration. The second randomized controlled trial also demonstrated a small nonstatistically significant difference in skin scores (−4.9; $p < 0.17$) between the MTX-treated and the placebo group after 12 months of weekly oral therapy [46].

T-cell-targeted immunotherapy

Cyclosporine A (CsA) primarily exerts its immunosuppressive function by interfering with T-cell production of IL-2 and other proinflammatory cytokines. This effect results from the inhibition of calcineurin, a key molecule for the activation of the nuclear factor for activated T cells (NF-AT) – the main transcription factor for IL-2 [25]. Experimental data have also demonstrated that CsA enhances the expression of collagenase in dermal fibroblasts, thus suggesting its potential antifibrotic effect [47]. The efficacy of CsA in chronic graft-versus-

host disease (GVHD), a condition secondary to recipient tissue damage by donor alloreactive T cells and often characterized by a peculiar progressive skin fibrosis, has prompted consideration of this drug for the treatment of SSc [48]. In a small 48-week open-label study, SSc patients treated with CsA demonstrated a significant response with a 36% decrease in skin scores ($p < 0.004$), although dose-limiting side effects were frequent, including abnormal increment of serum creatinine in 80% of patients [49]. In a 12-month randomized trial comparing treatment with iloprost alone or in combination with CsA, a significant improvement of skin involvement as measured by plicometry ($p = 0.008$) and a significant decrease in IL-6 levels ($p = 0.004$) were reported in the CsA-receiving group [50]. Some beneficial effects of CsA on skin fibrosis, as measured by subjective physician assessment of skin tightness, have also been shown in a retrospective analysis of 16 SSc patients treated for an average of 8 months [51]. However, in half of these patients hypertension was induced or exacerbated by CsA, and in two cases renal toxicity with increased creatinine levels occurred. In the same study, eight patients who failed or were intolerant to treatment with CsA were subsequently started on another calcineurin inhibitor, tacrolimus, with an unclear benefit but apparently less side effects. Denton *et al.* reported an onset of acute hypertensive renal failure in three patients (out of eight) with dcSSc treated with CsA [52]. Overall, the effect of CsA in SSc, as demonstrated by these studies, was modest and limited to skin involvement. For this reason and in view of its narrow therapeutic range and substantial side-effects profile (i.e., renal toxicity and hypertension), the use of CsA in SSc has been mostly avoided.

Sirolimus (rapamycin) belongs to a novel class of immunosuppressive drugs known as proliferation signal inhibitors, or mammalian target or sirolimus (mTOR) inhibitors. In the cytoplasm, sirolimus binds to FK-binding protein 12 forming a complex that inhibits mTOR. This results in a significant decrease in the T- and B-lymphocyte response to cytokines and activation stimuli [53,54]. In addition, experimental evidence has demonstrated that mTOR inhibition can independently decrease collagen production from dermal fibroblasts, suggesting a potential role for its use in fibrotic skin disorders [55]. Sirolimus has been primarily used for the prevention of transplant rejection, but there are emerging reports of its application in rheumatic diseases [56,57]. Few cases of SSc or idiopathic pulmonary fibrosis treated with sirolimus have been reported [58–60]. More recently, a 48-week single-blind randomized Phase I study of sirolimus versus MTX has been published [61]. The primary goal of this small pilot study was to assess the drug safety in 18 patients with early dcSSc, randomized to receive weekly oral MTX (target dose 20 mg/week) or sirolimus (to maintain a serum level of 5–15 ng/ml). In general, sirolimus did not show any striking toxicity, with the exception of intractable hypertriglyceridemia, which led one patient to withdraw from the study. The mRSS and disease activity scores improved from baseline with each treatment but did not significantly differ between the two groups at the end of the study. Interestingly, the FVC significantly declined from baseline (10.5 ± 6.6; $p = 0.05$) in patients treated with sirolimus. Larger studies are clearly necessary to establish the efficacy of sirolimus for the treatment of SSc-related manifestations. Several reports of lung toxicity in transplant recipients maintained on mTOR inhibitors also suggest that a more careful assessment concerning the safety of these drugs is needed [62–64].

Antithymocyte globulin (ATG) therapy represents another established approach to directly target T cells. This therapy is based on the intravenous administration of polyclonal IgG antibodies obtained from animals immunized with human thymocytes. ATG has been long used in organ transplants to prevent rejection and to treat other complications, such as GVHD and aplastic anemia [65]. More recently, ATG has been employed as a treatment for organ- and nonorgan-specific autoimmune diseases [66,67]. There is evidence that the therapeutic efficacy of ATG does not rely only on T-cell depletion. In fact, this drug has also shown the ability to interfere with lymphocyte transendothelial trafficking to cause

concurrent B-cell depletion and to induce regulatory T-cell function [68,69]. In a small open-label trial, administration of a single course of ATG (10 mg/kg for 5 days) to ten patients with early SSc did not demonstrate efficacy in improving skin or pulmonary disease [70]. In another study, 13 patients with early dcSSc were given ATG as induction therapy, followed by 12 months of MMF [71]. Although the mean skin score significantly decreased from the baseline (mRSS from 28 ± 3.2 to 17 ± 3.0; $p < 0.01$) during the study period, no significant change in FVC was detected. One patient died from scleroderma renal crisis shortly after ATG treatment, and five (38%) experienced a serum sickness reaction, raising concerns about this drug's safety.

Basiliximab is a chimeric monoclonal antibody directed to the α-chain of the IL-2 receptor (CD25) of T cells, inhibiting their activation and proliferation [72]. It is frequently used as an alternative to ATG for induction therapy in solid organ transplantation, particularly kidney, demonstrating comparable efficacy and less side effects [73]. In a patient with progressive dcSSc, the addition of basiliximab to intravenous CYC and oral prednisolone was well tolerated and prompted some further improvement of skin fibrosis [74].

Abatacept is a recombinant CTLA4-Ig fusion protein that interferes with the costimulation of T cells, promoting a negative regulation of their effector function. This drug has already been approved for the treatment of rheumatoid arthritis and is currently under investigation in several other autoimmune disorders [75,76]. A randomized placebo-controlled trial in dcSSc patients is underway [201].

The small molecule halofuginone, an analog of the plant alkaloid febrifugine, combines antifibrotic properties (via TGFβ-signaling inhibition) with the ability to inhibit T-lymphocyte differentiation to the Th17 phenotype, a cellular subset with important proinflammatory function in autoimmune disorders [77–79]. Topical application of 0.01% of halofuginone in SSc skin disease has been tested in a pilot study with encouraging results [80].

Alefacept, a recombinant human leukocyte function-associated antigen (LFA)-3 and IgG1 fusion protein, exerts its immunosuppressive function by blocking the costimulatory interaction between leukocyte function-associated antigen-3 (antigen-presenting cells) and CD2 (memory effector cells). Its main effect is the prevention of T-cell activation and proliferation. Efficacy of alefacept for the treatment of psoriasis, a T-cell-mediated skin disease, has been reported [81]. Off-label use in SSc has been suggested, and its safety and biologic efficacy has been demonstrated in a small pilot study of eight patients [82,83].

Extracorporeal photoimmunotherapy or photopheresis (ECP) has been used to treat T-cell-mediated diseases, such as cutaneous T-cell lymphomas, Sezary syndrome and GVHD for the past 20 years [84–88]. This procedure consists of irradiating leukocytes separated through apheresis with UVA light after exposing them to a photosensitizer (either through oral intake of 8-methoxypsoralen or by direct addition of a similar agent to the collected cells) followed by their reinfusion into the patient [89]. Multiple mechanisms have been postulated to explain the therapeutic efficacy of ECP, including removal of malignant or autoreactive T-cell clones, maturation of dendritic cells and the induction of regulatory T cells [90–92]. ECP has been successfully applied to the treatment of autoimmune skin conditions, such as bullous phemphigoid [93]. French *et al.* have shown the ability of ECP to remove clonally expanded T-cell populations in the peripheral blood of SSc [94]. In a multicenter single-blinded trial, 79 SSc patients were randomized to receive monthly ECP or D-penicillamine [95]. After 6 months of treatment, response to therapy, defined as 15% or more improvement in skin score, was significantly higher in the ECP group (68% of patients) compared to the D-penicillamine group (32%; $p = 0.02$). The difference was not

significant at 10 months. Some improvement of skin fibrosis was demonstrated in six out of 16 (35%) SSc patients treated with ECP for 6–45 months [96]. These positive results have not been corroborated by the only randomized double-blind, placebo-controlled trial of ECP [97]. Knobler *et al.* assigned 64 patients with early SSc to either active or sham ECP treatment administered monthly for 1 year. Although the skin score improved among the ECP-treated subjects at 12 months compared to baseline ($p = 0.008$) the changes were not significantly different between the two groups ($p = 0.129$). The modest benefits demonstrated by ECP and the lack of efficacy on internal organ manifestations have limited the use of this approach in SSc.

B-cell-targeted immunotherapy

Rituximab is a chimeric IgG1 monoclonal antibody directed against CD20, a surface antigen expressed on early pre-B and mature B cells. Selective depletion of $CD20^+$ B cells is mainly achieved through complement-mediated and antibody-dependent cellular cytotoxicity as well as the induction of B-cell apoptosis [98–100]. The use of rituximab has been investigated in several autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, Wegener's granulomatosis and other vasculitides, showing benefit and evidence of clinical response [101–105]. Despite the encouraging results, the dosing of this medication, the intervals between infusions and the overall safety have not yet been fully established. The use of rituximab in SSc has been initially tested in two small open-label uncontrolled trials [106,107]. In both studies, the administration of a single course (two doses of 1000 mg administered intravenously) of rituximab effectively depleted circulating and dermal B cells in patients with early dcSSC. However, the results regarding improvement of skin involvement were conflicting. In the study by Lafyatis *et al.*, the skin score did not exhibit any significant change (mean change −0.37 mRSS; $p = 0.82$) in 15 treated dcSSc patients after 6 months of follow-up [106]. Conversely, Smith *et al.* reported a 43% skin score improvement (−10.5 mRSS; $p<0.001$) in eight patients after 24 weeks [107]. A recent pilot study randomized 14 dcSSC patients with ILD to treatment with rituximab plus standard therapy versus standard therapy alone for 1 year [108]. Rituximab was administered in two 4-week cycles (375 mg/m^2 per week) at baseline and then at 6 months. After 1 year of follow-up, the rituximab-treated patients, but not the controls, demonstrated significant improvement from baseline of their lung function (FVC: +7.5%, $p = 0.0018$; DLCO: +9.75%, $p = 0.017$) and skin score (−5.13 mRSS; $p < 0.001$). When the two groups were directly compared, a significant difference favoring rituximab was detected only in terms of their lung function. Although encouraging, these findings are limited by the extremely small sample size and the fact that the concomitant 'standard' treatment, which included other immunosuppressive drugs, was not equally distributed between the two groups.

In addition to B-cell depletion via CD20 (rituximab), other B-cell-targeted therapies are under consideration to treat rheumatologic disorders, such as rheumatoid arthritis and systemic lupus erythematosus. Among the most novel biologic therapies with ability to effectively suppress B-cell maturation, proliferation and survival are epratuzumab, belimumab and atacicept or TACI-Ig. Epratuzumab is an anti-CD22 monoclonal antibody [202]. Atacicept is a recombinant fusion protein that interferes with the function of B-lymphocyte stimulator (CD257) and a proliferation-inducing ligand (CD256) [109,110]. Belimumab is an anti-B-lymphocyte stimulator monoclonal antibody [111]. While these treatments offer the appealing property of further modulating the proinflammatory function of B cells without a radical depletion, their usefulness in SSc has not yet been studied.

Intravenous immunoglobulins

Intravenous immunoglobulins (IVIGs) is a preparation of pooled immunoglobulins obtained from a large number of healthy donors traditionally used as replacement therapy in primary and secondary immunodeficiencies [112]. When used at high doses (i.e., 2 g/kg monthly), IVIG has shown immunomodulatory and anti-inflammatory properties, and for this reason has been successfully employed to treat several immune-mediated disorders, including idiopathic thrombocytopenic purpura (ITP), hemolytic anemia, Guillain–Barre syndrome, chronic idiopathic demyelinating polyneuropathy, acute myasthenia gravis, dermatomyositis and vasculitis [113,114]. Experimental evidence suggests that this therapeutic effect may rely on the ability of IVIGs to interfere with complement activation, to neutralize autoantibodies and proinflammatory cytokines, and to regulate cellular effectors of the innate and adaptive immune responses [115,116]. Recent advances suggest that the interaction between normal or modified (i.e., sialylated) IVIG Fc fragments and their cellular receptors may be pivotal in modulating some of these functions [116,117]. IVIG has also demonstrated distinct antifibrotic activity in some animal models and has proven to be an effective treatment in other fibrotic disorders (i.e., scleromyxedema) [118,119]. Experience in SSc is limited to a few open-label investigations that have indicated uniformly that IVIG improves skin fibrosis in treated patients [120–124]. However, these studies report an overall limited number of patients and also present significant heterogeneity in terms of disease subtype (lcSSc and dsSSc) and disease duration (0.33–20 years). In addition, it is unclear how concurrent immunosuppressive therapies were managed in relation to the intervention. For this reason it is difficult to fully exclude that the observed skin thickness improvements were reflective of the natural course of the disease or secondary to the effect of other medications. Interestingly, in a small study of seven SSc patients, treatment with IVIG for 6 months has been effective in treating inflammatory and fibrotic joint symptoms, which were refractory to the underlying immunosuppressive therapy [124].

Other biological immunotherapies

Anti-TNF-α agents have been successfully used for more than a decade to treat inflammatory conditions, such as rheumatoid arthritis, spondyloarthropathies and Crohn's disease [125–127]. Their potential use and safety in fibrotic disorders has been the subject of significant debate [128]. In fact, experimental data have provided conflicting results regarding the role of TNF-α in regulating fibrogenesis. Traditionally, TNF-α has been considered to be an antifibrotic cytokine [129–131], and there have been some case reports describing the onset or exacerbation of fibrosing alveolitis in patients using anti-TNF agents [132,133]. Conversely, other studies have demonstrated profibrotic functions of TNF-α, evidence supported by *in vivo* animal models [134–137]. In a retrospective analysis, 18 SSc patients with concurrent inflammatory joint disease were treated for 2–66 months with etanercept, a recombinant soluble p75 TNF-α receptor [138]. The medication was well tolerated and provided excellent control of the articular manifestations. The mean skin scores improved ($p = 0.12$) and, importantly, no significant decline of lung function was observed (average change of predicted FVC: −1.4%; and DLCO: −5.1%). By contrast, an open-label study of 16 SSc patients with early progressive dcSSc receiving a chimeric monoclonal anti-TNF antibody (infliximab 5 mg/kg) did not show any significant improvement after 24 weeks of treatment in terms of skin involvement or lung function [139]. Biomarkers of collagen biosynthesis (aminoterminal propeptide), immunological activity (IL-2 receptor) and vascular damage (von Willebrand factor) declined at the end of the study, although statistical significance ($p = 0.03$) was reached only for aminoterminal propeptide. Notably, a high number of these patients (44%) experienced adverse events possibly related to infusion reactions, and several cases (33.3%) developed neutralizing anti-

infliximab antibodies, suggesting that concurrent administration of another immunosuppressive drug may be indicated.

TGFβ is a cytokine promoting fibroblast proliferation and differentiation in addition to upregulation of collagen and extracellular matrix synthesis [140]. The pivotal role of TGFβ in fibrogenesis and its potential relevance in SSc pathogenesis has made this cytokine an attractive target to develop novel disease-modifying therapies for this condition. A multicenter, randomized, placebo-controlled Phase I/II trial has been conducted in a cohort of early-stage dcSSc patients to evaluate the safety and tolerability of CAT-192, a recombinant human antibody against TGFβ [141]. While the skin fibrosis mRSS improved in the treated group, these changes were not significant compared to placebo and no other clinical benefit was detected. The low affinity of the CAT-192 antibody may suggest that higher doses are needed to obtain better results. However, concerns have been raised about achieving complete nonselective TGFβ blockade given the pleiotropic function of this cytokine and its role in maintaining immune tolerance synthesis [140]. New therapeutic strategies directly targeting mediators of TGFβ intracellular signaling are under investigation. In particular, small molecule tyrosine kinase inhibitors (i.e., imatinib and dasatinib) have shown promising results in animal models of SSc and lung fibrosis [142,143]. These drugs inhibit the tyrosine kinase activity of the Abelson (Abl)-kinases and PDGF receptors, thus interfering with important profibrotic pathways activated in SSc [144,145]. Imatinib mesylate has been reported to improve skin fibrosis in SSc-like disorders, such as nephrogenic systemic fibrosis and chronic GVHD [146–149]. In SSc, a few case reports have described the safe use of imatinib [150–152]. Several open-label trials with tyrosine kinase inhibitors in SSc are currently underway. The interim analysis of a Phase IIa single-center open-label study of 30 dcSSc patients treated with imatinib 400 mg orally daily demonstrated clinical and histological improvement of skin fibrosis [153]. Skin scores at 12 months decreased by 7.3 ± 4.6 ($p < 0.001$), and lung function significantly improved (increase in FVC from 84 ± 22 to $90 \pm 23\%$, $p = 0.039$; increase DLCO from 80 ± 21 to $88 \pm 27\%$, $p = 0.037$). Importantly, only 16 patients completed 1 year of treatment, and a significant number of adverse events were reported, including fluid retention (80%), nausea (73%), fatigue (53%) and elevation of creatine kinase (37%). Another study, a proof-of-concept, double-blinded, randomized control trial, was interrupted after 6 months due to poor tolerability of imatinib [154]. Only four of the ten active dcSSc patients enrolled were able to complete the 6 months of treatment. Adverse events were frequent and similar to those reported in the previous study. No clinical benefit was detected. Other tyrosine kinase inhibitors, such as dasatinib and nilotinib, are under consideration for use in SSc. While their Abl-kinase inhibition is more potent and has been confirmed in SSc dermal fibroblasts, their side-effect profile is apparently milder than imatinib [155,156]. A new selective TGFβ1 inhibitor (P144) is currently under investigation in a multicenter trial [203].

The discovery that neutralizing antibodies against CTGF can effectively suppress development of skin fibrosis in animal models has sparked interest to consider anti-CTGF therapy in SSc [157].

Treatment with alemtuzumab (CAMPATH-1H®), a monoclonal antibody targeting CD52 (protein present on the surface of mature T and B lymphocytes) has been reported to induce a rapid and sustained improvement of the skin score in a patient presenting with polyvinyl chloride-induced progressive dcSSc [158]. Its use in immune-mediated disorders has been mainly limited to multiple sclerosis where benefit has been shown, although infectious and immunologic adverse events have also been reported [159].

Cell-based immunotherapy

Autologous and allogeneic hematopoietic stem cell transplantation (HSCT) preceded by myeloor nonmyelo-ablative (immunoablative) conditioning regimens have been employed as possible therapeutic strategies for severe autoimmune disorders over the past decade [160–164]. This approach was initially prompted by anecdotal reports that underlying autoimmune manifestations improved or resolved in individuals undergoing HSCT for a hematologic malignancy [165–171]. Data collected from the European Group for Blood and Marrow Transplantation and the European League Against Rheumatism (EBMT/EULAR) Working Party on Autoimmune Diseases database demonstrated that among the 37 SSc patients treated with high-dose CYC followed by autologous HSCT (n = 35) or bone marrow transplant (n = 2) a remarkable and rapid improvement of the skin involvement was noted [172]. A significant decline of the skin score (>25% from baseline or 10% from maximum recorded) was achieved in 69% of patients, and the mean mRSS was already significantly improved from pretreatment baseline at 30 days. While no significant deterioration of the lung or other organ function was observed in the follow-up period, a relevant mortality rate of 17% directly related to the HSCT protocol was reported. To improve the safety of the procedure, newer and stricter exclusionary criteria as well as changes to the conditioning protocols (i.e., avoidance of total body irradiation or use of lung shielding) were implemented. As a consequence, in the subsequent report from the EBMT/EULAR registry, which included an additional 25 SSc patients (total n = 57), the transplant-related mortality was reduced to 8.7% [173]. This study detected a partial or complete response in 92% of patients at 6 months' follow-up, confirming that autologous HSCT treatment effectively prompts sustained improvement of SSc skin involvement. However, 35% of responders relapsed within 9 months (range: 2.2–48.7 months) after HSCT suggesting that additional immunosuppression or maintenance therapy may be needed in order to keep the treated SSc patients in remission. In the USA, a pilot Phase II single-arm trial with high-dose immunosuppressive therapy and autologous HSCT was conducted in 19 early dcSSc patients, reporting a treatment-related mortality of 16% [174]. This protocol did include total body radiation, CYC and ATG as part of the conditioning regimen, and lung shielding was applied in 58% of the patients. At a median follow-up of 15 months, 79% of the patients were alive with a projected 2-year survival rate of 78.9%. The extension of this multicenter study included a total of 34 dcSSc patients and was conducted without modification of the conditioning protocol [175]. Treatment-related mortality remained significantly high (23%). The mean decrease of the skin score was statistically significant throughout the follow-up period (−70.3% at the final evaluation; $p < 0.001$). A nonsignificant increase of the FVC was noted at the end of the study (2.11%; $p = 0.50$), while the DLCO dropped by an average of 6.04% ($p = 0.05$). Among those who survived at least 1 year after the HSCT, 17 (63%) had sustained responses at a median follow-up of 4 years. The main assumption of the myeloablative approach is that the conditioning regimen, normally based on high-dose immunosuppression associated in some cases with specific lymphocyte depletion and/or total body irradiation, is able to eradicate autoreactive immune cells while at the same time 'resetting' the dysfunctional immune system and creating the conditions for a new immune homeostasis achieved by the reinfusion and differentiation of uncommitted autologous bone marrow precursors. The evidence has not yet fully supported this hypothesis as evidenced by the sizable number of disease relapses at variable points in time following HSCT, particularly when no maintenance immunosuppression was instituted. In addition, less aggressive (and less toxic) nonmyeloablative (immunoablative) HSCT protocols have demonstrated similar results [176].

Based on these previous experiences, two multicenter, prospective, randomized controlled trials of high-dose immunosuppressive therapy and HSCT versus monthly pulsed CYC are now underway: the Scleroderma Cyclophosphamide or Transplant (SCOT) trial in the USA

and the Autologous Stem cell Transplantation International Scleroderma (ASTIS) in Europe [177]. These studies will help to define with greater accuracy the clinical usefulness of this therapeutic intervention and will clarify whether the treatment-related toxicity can be effectively contained.

Conclusion & future perspective

The treatment of SSc remains a significant challenge despite the advances made in understanding its key pathogenetic events over the past decade. The contribution of the immune system to the initiation and propagation of the disease process has long been recognized. Traditional immunosuppressive treatments have demonstrated some efficacy during early skin involvement and active lung inflammation, but they do not appear to provide benefits during later phases of the disease. In addition, they are associated with significant morbidity and mortality.

More recently, mechanisms linking specific immune events to the development of vascular injury and tissue fibrosis in SSc have started to be elucidated. This has opened the possibility of new treatments directed toward specific molecular or cellular effectors involved in the disease pathogenesis. Targeted immunotherapies have been successfully introduced to treat many autoimmune disorders, particularly in the field of rheumatic diseases, leading to a substantial improvement of clinical outcomes both in terms of efficacy and safety. It can be expected that the number of monoclonal antibodies or small molecules that can potentially be used in SSc will continue to grow in parallel with a deeper understanding of the biology of this disease. Whether these agents will be used as standalone therapies is still unclear. More likely, the combination of these new immunomodulatory strategies with emerging antifibrotic and vasoprotective drugs will be more effective.

The rarity of SSc and the heterogeneity of its clinical presentation have undermined the power of previous interventional studies to reach conclusive evidence regarding treatment efficacy. Ideally, no treatment should be accepted as standard of care in clinical practice unless it is proven to be effective in a randomized control trial, which provides the most compelling evidence for efficacy when evaluating new therapies. With this purpose, over the past few years, an increasing number of national and international academic centers have joined into larger randomized control trials designed on the basis of accepted diagnostic and therapeutic guidelines. These are starting to provide more rigorous and clinically meaningful results. In the next decade, evidence-based use of nonselective immunotherapies and the translation of new discoveries concerning the cellular and molecular basis of SSc into targeted treatments will grant an unprecedented opportunity to effectively treat SSc and its manifestations.

Executive summary

Scleroderma immunopathogenesis

- Immune activation involving humoral and cellular events appears to be a fundamental step for disease initiation and propagation.
- Skin and lung fibrosis are preceded by early mononuclear infiltrates, in particular T cells. Vascular injury is, at least in part, mediated by an immune activation.
- During later phases of systemic sclerosis (SSc), inflammatory events become less intense and the immune response acts as a low-grade amplifier of fibrogenesis and microangiopathy, presenting a significant therapeutic challenge.

Nonselective immunotherapy

- Very few randomized control trials are available. Despite evidence for the modest benefit on lung function in SSc, cyclophosphamide (CYC) remains the drug of choice for interstitial lung disease and early active skin involvement.
- Mycophenolate mofetil is less toxic than CYC and has been used with some favorable results to treat SSc–interstitial lung disease and skin disease in small observational studies.
- Methotrexate is frequently used in SSc to treat associated inflammatory arthritis and myositis.

T-cell-targeted immunotherapy

- Use of cyclosporine in SSc has been limited by modest efficacy for the treatment of skin disease and substantial side effects (renal toxicity).
- Sirolimus is a promising new immunosuppressive drug with antifibrotic properties also awaiting larger trials to properly define its efficacy and safety in SSc.
- Novel biologics (e.g., basliximab, abatacept and alefacept) with the ability to interfere with T-cell activation and effector function are of interest for SSc.

B-cell-targeted immunotherapy

- B-cell-depletion therapy with rituximab to treat pulmonary and skin SSc manifestations has provided some encouraging results in few small open-label studies. Larger prospective trials are needed to determine the clinical efficacy of this approach.

Intravenous immunoglobulins

- Intravenous immunoglobulins have shown efficacy in several immune-mediated disorders and have demonstrated antifibrotic properties in animal models. Possible benefits for SSc fibrotic skin and joint manifestations have been suggested by a few open-label investigations, but this awaits confirmation in larger studies.

Biological immunotherapies

- Anti-TNF-α therapies can be useful to control inflammatory joint manifestations in SSc, but have shown no benefit for skin or lung involvement.
- No exacerbation of fibrotic manifestations has been reported following anti-TNF-α drug therapy.
- TGF-β plays a pivotal role in fibrogenesis and pathogenesis of SSc. In a multicenter randomized control trial, treatment with recombinant anti-TGF-β antibody was well tolerated; however, it did not show efficacy.
- Tyrosine kinase inhibitors (e.g., imatinib) interfere with profibrotic pathways operating in SSc. While prolonged treatment with imatinib may be necessary to yield measurable clinical benefits, substantial toxicity has limited its use thus far in SSc.

Cell-based immunotherapy

- Rapid and sustained improvement of severe fibrotic SSc skin involvement can be achieved with autologous hematopoietic stem cell transplantation.

- Additional immunosuppression or maintenance therapy may be needed to keep patients in remission and retain clinical benefits.
- Morbidity and mortality remains elevated among SSc patients treated with hematopoietic stem cell transplantation, even though modification of conditioning protocols has improved overall safety.

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▪▪ of considerable interest

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Table 1

Immunotherapeutic treatments in systemic sclerosis.

Therapeutic category	Drug	Mechanism of action	Dosage/formulation	Ref.
Nonselective immunotherapy	CYC	Alkylating agent, direct bone marrow and mature lymphocyte cytotoxicity	1–2 mg/kg p.o. daily 600 mg/m^2 iv. monthly	[27–30]
	Mycophenolate mofetil	Purine synthesis (IMPDH) inhibitor, antiproliferative	500–1500 mg p.o. twice daily	[36–40]
	Azathioprine	Purine synthesis inhibitor, antiproliferative	100 mg or 2–3 mg/kg p.o. daily	[30,41–43]
	Methotrexate	Antimetabolite (dihyrdofolate reductase inhibitor), antiproliferative and cytotoxic	10–25 mg p.o. or im. weekly	[45,46]
T-cell-targeted immunotherapy	Cyclosporin A	Calcineurin inhibitor, interference with T-cell activation and IL-2 production	2.5–5 mg/kg p.o. daily	[49–51]
	ATG	T-cell depletion, suppression of lymphocyte trafficking and activation	3–10 mg/kg iv. daily for 5 days	[70,71]
	Extracorporeal photopheresis	Removal of autoreactive T-cell clones; induction of regulatory T cells	6–453 cycles (one cycle = two sessions on 2 consecutive days, usually monthly)	[95–97]
	Sirolimus (rapamycin)	mTOR inhibitor, suppression of T and B lymphocyte activation	6 mg p.o. daily, adjusted to serum level 5–15 ng/ml	[61]
B-cell-targeted immunotherapy	Rituximab	Chimeric IgG1 monoclonal anti-CD20 antibody	1000 mg iv. administered 2 weeks apart; 375 mg/m^2 weekly for 4 weeks	[106–108]
Intravenous immunoglobulins	IVIG	Inhibition of complement activation, antibody neutralization, induction B-cell apoptosis, Fc receptor-dependent immunomodulation	2 g/kg iv. monthly (usually administered over 5 days)	[120–124]
Biological immunotherapy	TNFα inhibitors	Recombinant soluble p75 TNF-α receptor	25 mg sc. twice weekly or 50 mg sc. once weekly	[138]
	Infliximab	Chimeric monoclonal anti-TNF antibody	5 mg/kg iv. every 8 weeks	[139]
Antifibrotic therapy	CAT-192	Recombinant human anti-TGF-β antibody	0.5–10 mg/kg iv. every 6 weeks (total of four infusions)	[141]
	Imatinib mesylate	Inhibition of tyrosine kinase activity of abl-kinases and PDGF receptors	400 mg p.o. daily	[153,154]
Cell-based immunotherapy	Autologous HSCT	Myeloablation or myelosuppression (immunoablative), cytotoxicity autoreactive and immune effector cells, immune reconstitution with uncommitted functional bone marrow precursors	Conditioning regimens: TBI (800 cGy ± lung shielding at 200 cGy), CYC 120 mg/kg iv. and ATG 90 mg/kg iv., prednisone 0.5 mg/kg/day p.o. (McSweeney, Nash) CYC 150–200 mg/kg iv., ATG iv. (not specified), or ATG ± TLI or TLI or CAMPATH; or alternate regimen (Farge) CYC 200 mg/kg iv., ATG 7.5 mg/kg iv. (Oyama)	[172–176]

ATG: Antithymocyte globulin; CYC: Cyclophosphamide; HSCT: Hematopoietic stem cell transplantation; im.: Intramuscular; IMPDH: Ionosine 5′ monophosphate dehydrogenase; iv.: Intravenously: p.o.: Orally; sc.: Subcutaneously; TBI: Total body irradiation; TLI: Total lymphoid irradiation.