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REVIEW

Immunotherapy of systemic sclerosis

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ABSTRACT

Systemic sclerosis (SSc) is a chronic systemic disease characterized by microvasculopathy, immune activation, and extensive collagen deposition. Microvasculopathy and immune activation occur very early in the disease process. Evidence from animal models and in vitro studies indicate that T-cells and B-cells activate fibroblasts to produce collagen. Traditional immunosuppressants, cyclophosphamide(CyP), methotrexate(MTX), and more recently mycophenolate mofetil(MMF), may prove more effective if used very early in the disease course. These drugs showed some benefit in skin (MTX, CyP, MMF) and lung function (CyP, MMF). Biologicals, such as intravenous immunoglobulin (IVIg), belimumab(Beli), tocilizumab (TCZ), abatacept(Aba), rituximab(RTX) and fresolimumab(Fresu) appear promising as they exhibited some benefit in skin (IVIg, Beli, TCZ, Aba, RTX, Fresu), hand function (IVIg), and joints (IVIg, TCZ, Aba). Autologous stem cell transplantation showed the best therapeutic efficacy on skin and internal organs, and looks very promising, as modification of transplantation immunosuppression is decreasing the early high mortality.

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Introduction

Systemic sclerosis (SSc) is a chronic connective tissue disease (CTD), which affects skin, blood vessels, lungs, heart, kidneys, gastrointestinal (GI) tract and musculoskeletal system. It is characterized by three cardinal features: early microvascular obliterative changes, activation of the immune system and widespread fibrosis of skin and internal organs. Involvement of internal organs results in significant morbidity and mortality. Microvascular changes are exemplified by Raynaud's phenomenon (RP) and microvascular injury seen as nailfold capillaroscopy abnormalities, whereas immune activation is exemplified by SSc-related autoantibodies (auto-Abs).[1–3]

Systemic sclerosis affects all races and may be diagnosed at any age although most cases develop in individuals aged 20–60 years. As data continue to gather from around the world, it is shown that while the incidence of SSc exhibit remarkable variation across different geographic regions (ranging 2–23 cases per million), it appears to rise over the past three decades. Prevalence is also documented to span between 46–655 cases per million among different centers.[4,5] Female predominance is evident among cases with limited SSc, while diffuse SSc appear to affect males and females at more comparable rates.[2–6] SSc is considered to be a chronic, gradually deteriorating disease across several months to years. Some cases can stabilize for prolonged periods of time while others, primarily with diffuse disease, show a fulminate clinical course with detrimental consequences within few months. Mortality as well morbidity among patients with scleroderma is increased. Ten-year cumulative survival rate was found 66% during the 1990s.[7] Major morbidity is related to the type and extent of internal organ involvement, such as pulmonary fibrosis and/or pulmonary hypertension that often lead to severe dyspnoea and oxygen dependence.[6] GI tract involvement includes both the upper (common) and the lower part (less common); it may also be quite severe leading to malnutrition and death.[8] Infections also play significant role for the increased morbidity and mortality of patients with SSc. Propensity to infections is derived from both poor functional status and immunosuppressive treatment. Hand dysfunction due to tight skin, joint contractures and ulceration of the fingertips represent a common disabling factor among patients with SSc, which also leads to significant morbidity due to pain, frequent injuries, gangrene secondary to ischemia and self-amputations.[6] In overall diffuse skin disease, male gender, older age at onset, cardiopulmonary involvement, renal crisis and the absence of Raynaud's phenomenon as the initiating clinical symptom represent bad prognostic factors.[9,10]

Vascular abnormalities and immune abnormalities appear early in the disease course and are likely to drive the pathogenetic cascade of the disease. SSc-related auto-Abs, such as anti-topoisomerase I (anti-Topo; formerly anti-Scl70), anti-centromere (ACA), and anti-RNA polymerase III auto-Abs, appear before, and sometimes years before clinical fibrosis.[2] Longitudinal skin biopsies from patients with SSc reveal inflammatory infiltrates early before histological fibrosis, but as the disease progresses inflammatory infiltrates greatly diminish and fibrosis dominates the histological picture.[11] Pro-fibrotic cytokines, such as transforming growth factor (TGF)β, are considered pivotal for the disease pathogenesis. Evidence from animal models and in vitro studies indicates that T cells through cell contact, and cytokines activate fibroblast to produce collagen.[3,12] Increased levels of T cell cytokines, including the pro-fibrotic IL-4 and IL-13 (Th2 cells),

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are seen in peripheral blood from SSc patients.[13,14] Although aberrations in the expression of individual cytokines may be shared among several different diseases, it is obviously the fine combination of several abnormalities that lead to systemic collagen disposition, a feature unique to SSc among other systemic autoimmune diseases underscoring the complexity of the cellular controls operating in enhancing or suppressing the profibrotic response.[15,16] Mononuclear cell infiltrates, consisting mainly of T cells and macrophages, appear very early in the disease process.[17] B cells are hyperactivated in SSc, as indicated by the overexpression of the stimulatory CD19 receptor and impairment of the inhibitory CD22 receptor.[18] B cells contribute to disease pathogenesis by activating B cells via cell contact, cytokines and autoantibodies.[17,18] Some SSc-associated autoantibodies, such as anti-platelet-derived growth factor receptor antibodies, and anti-angiotensin II type 1 receptor (AT1R) antibodies, are agonistic antibodies and can cause collagen production and vasoconstriction, respectively.[18–20] B cells also can act as antigen-presenting cells to T cells and induce dendritic maturation that promotes profibrotic Th2 response.[18] B cells through cell contact activate fibroblasts isolated from SSc patients to produce collagen and profibrotic growth factors IL-6, and TGFβ1.[21]

It is thus essential to target immune abnormalities early before fibrosis and organ failure develops, where available treatments are largely ineffective. New classification criteria for SSc have been recently developed, that could help diagnose SSc early, and facilitate early recognition of SSc and offer opportunities for early therapeutic intervention.[22,23]

Immunotherapy includes general immunosuppression and therapies targeting specific molecules involved in T cell and B cell survival and function (targeted therapies). Data on targeted therapies, such as biologics in the treatment of patients with SSc are emerging. However, the new classification criteria of SSc will help to further explore the efficacy of timely intervention with "traditional" treatments. This review summarizes currently available immunotherapeutic agents for SSc.

Immunotherapies

General immunosuppression

1. **Cyclophosphamide.** Cyclophosphamide (CyP) is an alkylating and cytotoxic immunosuppressive agent, and, therefore, a general immunosuppressive drug. CyP represents the most widely used and studied therapy for SSc-associated interstitial lung disease (SSc-ILD). CyP can be administered either orally on a daily basis or by intravenous infusions every two to four weeks for several months. Numerous uncontrolled studies and two randomized controlled trials (SLS I and FAST)[24,25] showed some efficacy of CyP in SSc-ILD.[26] In early diffuse SSc, a prospective trial (ESOS – European Scleroderma Observational Study) included 326 patients from 50 centers (19 countries) and clinicians selected the therapeutic protocol of their choice. The observational period was 24 months. Sixty-five patients received methotrexate, 118 MMF, 87 CyP and 56 no immunosuppressant treatment. CyP was inferior to methotrexate in skin improvement, but it had the best results in Forced Vital Capacity (FVC), especially in those with pulmonary fibrosis in High-Resolution (HR)CT (MTX -2, MMF 3.2, CyP 7.4).[27] In an effort to further characterize which patients would benefit from CyP administration, plasmin-α2-plasmin inhibitor complex (PIC) – a potential biomarker of SSc vasculopathy – was measured in the serum of patients with SSc-ILD. Increased levels of PIC were correlated with active lung disease and higher efficacy of CyP.[28] CyP is usually given for a maximum of 6 months followed by milder forms of immunosuppression, such as methotrexate or azathioprine. Adverse effects of CyP include nausea and vomiting, bone marrow suppression, increased risk of infections, haemorrhagic cystitis, and bladder cancer.
2. **Methotrexate.** Methotrexate (MTX) inhibits dihydrofolate reductase, an enzyme required for DNA synthesis. It also causes extracellular release of adenosine that exerts immunomodulating effects. Two small, randomized, controlled studies of early SSc, and their re-analysis, showed that MTX, used in a relatively low dose (1015mg/w), improved skin score and hand function.[29–31] Higher doses of MTX (2025mg/w), which are generally a standard, first choice of therapy for rheumatoid arthritis, have been used in a prospective, observational cohort study, which showed statistical significant reduction in mRSS at 12 months compared to placebo.[27] Adverse effects of MTX include bone marrow suppression, gastrointestinal upset, hair loss, and liver fibrosis. Lung injury is also a concern, especially in patients with lung fibrosis.[32]
3. **Azathioprine.** Azathioprine (AZA) is a purine analog that inhibits DNA synthesis. AZA has been used as maintenance therapy in SSc-ILD after initial therapy with CyP.[25] In a randomized, open-label trial of oral AZA (2.5 mg/Kg/day) versus oral CyP in early diffuse cutaneous SSc, AZA showed no efficacy on skin thickness and pulmonary function,[33] whereas a retrospective study reported effectiveness of AZA in stabilizing lung function and improvement of mRSS.[34] Adverse effects of AZA include bone marrow suppression, hepatotoxicity and gastrointestinal upset.
4. **Mycophenolate Mofetil.** Mycophenolate mofetil (MMF) is an inactive prodrug of mycophenolic acid that inhibits inosine monophosphate dehydrogenase and, therefore, the proliferation of both T cells and B cells. Several retrospective or openlabel prospective studies in SSc and SSc-ILD have shown that MMF improved skin score and stabilized pulmonary function.[35–37] More importantly, it improved a 5-year survival. Recently a randomized, double-blind, parallel group trial that compared 2 years of oral MMF (target dose 3gr/day) to oral CYP (2 mg/kg/day) for 1 year followed by placebo was conducted.[38] Even though this study failed to meet its primary-end point of MMF superiority on lung function over CYP at 24months, an improvement of FVC, comparable to CYP, was clearly observed.[38,39] In the same study, MMF treatment (as well as CYP) improved skin score.[38,40] MMF is well tolerated and associated with less toxicity than

CYP.[38] Adverse effects of MMF include bone marrow suppression and increased risk of infections.

5. **Autologous Stem Cell Transplantation.** The process of haematopoietic stem cell transplantation (HSCT) eliminates autoreactive T cells and B cells. In autologous HSCT, haematopoietic stem cells (HSCs) are collected from a patient, who then receives strong immunosuppression, including CyP, to destroy immunocytes.

Finally, the patient receives his/her own HSCs to repopulate his/her bone marrow. In SSc patients, HSCT reverses the Th2 cell profile, producing the profibrotic IL-4 and IL-13, into Th1 cell profile, producing the anti-fibrotic interferon [IFN]γ. This turnaround is estimated to last at least 3 years and is associated with substantial skin improvement.[41] Because high-dose myeloablative regimen was associated with high frequency of early mortality with no superior efficacy compared to nonmyeloablative HSCT,[42] less intense non-myeloablative regimen is recommended. In non-randomized studies, autologous HSCT showed substantial efficacy in up to 90% of patients improving skin score and histological fibrosis and stabilizing the internal organ function up to 7 years after the transplantation.[43,44] It may also regenerate capillaries and improve microcirculation, as seen in nailfold capillaroscopy and histochemistry.[45,46] In an open-label randomized trial, autologous non-ablative HSCT was superior to monthly pulse CyP, improving skin score and lung function that persisted for up to 2 years.[47] Similar results were shown in a more recent multicentre RCT that included 156 patients.[48,49] A randomized trial in patients with severe scleroderma compared myeloablative HSCT to CyP, showed long term benefits in the transplantation group. These patients had better event-free and overall survival rates, observed after 2 years, at a cost of increased mortality.[50] Adverse effects include early mortality, increased risk of infections, and the development of new (secondary) autoimmune diseases, such as myasthenia gravis. Secondary autoimmune diseases occur in about 3.9% of HSCT cases. Therefore, ASCT should be reserved for carefully selected patients, as patients with rapidly progressing disease.

In Table 1 current use of general immunosuppressive agents in the treatment of patients with SSc is presented.

Treatment with immunosuppressants should be introduced early in SSc. Up to few years back, treatment of SSc has been applied to patients fulfilling the 1980 ACR classification criteria for SSc,[51] which are based on clinical features that are the sequel of the disease. These criteria included one major criterion (scleroderma proximal to MCP and/or MTP joints) and three minor criteria (sclerodactyly, digital ulcers, bibasilar pulmonary fibrosis). However, by that time, a patient has excess collagen and other extracellular matrix deposition in the skin and internal organs. At this stage of the disease, treatment is largely ineffective. The new EULAR/ACR 2013[22] criteria help early diagnosis of SSc, before the development of fibrosis in internal organs that allow the introduction of immunosuppressive medications. According to these criteria, a patient with Raynaud, SSc-related autoAbs [antitopoisomerase I (Scl70), anti-centromere autoAb, anti-RNA polymerase III], abnormal nailfold capillaries and puffy hands would have SSc. However, studies report preclinical internal organ involvement in pre-scleroderma patients. In a cohort of patients with very early diagnosis of SSc (VEDOSS) (RP, puffy fingers, ANA plus typical capillaroscopy abnormalities and/or SSc-associated autoantibodies) and a mean duration of disease 7.1 years, pulmonary disease (fibrosis or ground glass opacities on high resolution CT scan or DLCO<80% predicted) and/or lower oesophageal sphincter dysfunction was present in the majority of patients.[52] There seems to be a window of opportunity for effective therapy for SSc, and this appears to be confined to pre-scleroderma stage of the disease which in our view is the inflammatory phase of the disease, whilst the later phases, healing predominates with collagen matrix laying. Currently, immunosuppressants are prescribed according to disease manifestations, namely mild immunosuppressants for mild manifestations and strong immunosuppressants for life/organ threatening manifestations. If there was a biomarker with high predictive value for internal organ manifestations in SSc, then even strong immunosuppression might be justified early. However, it is time to consider and prescribe mild immunosuppression in RP patients with typical nailfold capillaroscopy changes and autoAbs in a well-monitored environment.[23]

Targeted therapies

B1. Biological therapies

1. **Intravenous immunoglobulin.** Intravenous immunoglobulin (IVIg) is a human polyspecific IgG (presented

Table 1. General Immunosuppressive drugs used in the treatment of systemic sclerosis.

Drug	Mechanism of Action	Recommendation/Use in SSc	*References*
Cyclophosphamide (CyP)	Alkylation of DNA, Cytotoxic	- primarily initial treatment in ILD - orally 1–2mg/kg/day or IV pulses every 2–4 weeks - duration 6mo	RCT: *24,25* Other: *27,28*
Methotrexate (MTX)	Inhibition of dihydrofolate reductase (Inhibition of DNA synthesis) Adenosine extracellular release	- primarily for skin disease - 10–25mg/week	RCT: *29,30* Other: *27*
Azathioprine	Inhibition of DNA synthesis	- Maintenance treatment for ILD - Alternative to MTX for skin disease - 2.5mg/kg/day	RCT: *25* Other: *34*
Mycophenolate Mofetil	Inhibition of inosine monophosphate-DH Inhibition of T, B cells proliferation	- Maintenance treatment for ILD - Alternative to MTX for skin disease - 2–3 g/day	RCT: *38* Other: *35–37, 39,40*
Autologous Stem Cell Transplantation *(in combination with CyP)*	Elimination of autoreactive T and B cells	- For severe lung and skin disease	RCT: *48,50* Other: *43–47*

ILD: Interstitial Lung Disease, RCT: Randomized Controlled Trial, DH: dehydrogenase.

as monomeric or multimeric forms) and derives from the plasma of thousands healthy individuals (3,000-80,000).[53] IVIg has been increasingly used during the last decades for an growing number of systemic immune-mediated and heterogeneous inflammatory diseases The mechanism of high-dose IVIg remains unclear, but probably works in multiple fronts, such as blocking the binding of serum immunoglobulins, B cell surface immunoglobulins, and T cell antigen receptors to their respective antigens.[54] IVIg reduced skin fibrosis and inhibited IL-4 and TGF-β production in tight skin (TSK) mice.[55] In two small open-label studies in patients with SSc, IVIg reduced histological skin fibrosis and joint pain and improved hand function.[56,57] A recent double-blind multi-center RCT in 63 patients with diffuse cutaneous SSc (dcSSc) concluded that IVIg improved skin score especially after multiple courses.[58] Serious adverse reactions are rare and include arterial thrombosis, severe anaphylaxis, aseptic meningitis, and renal tubular crisis. Most adverse effects are mild and are limited to nausea, rhinitis, asthma, chills, low-grade fever, myalgia, and migraine headache. The variables potentially affecting the risk and intensity of adverse events include patient's age, cardiovascular or renal disease, dyslipidemia, diabetes and IgA deficiency with anti-IgA antibodies.[59]

2. **Belimumab** – Belimumab is a human monoclonal antibody currently approved for the treatment of systemic lupus erythematosus (SLE). It inhibits B-cell activating factor (BAFF), also known as B lymphocyte stimulator (BLyS), which is a B cell modulator and maturation factor. High BAFF expression levels in skin biopsies were observed in a tight-skin mouse model and the extent of skin fibrosis, as well as BAFF levels, IL-6 and IL-10 production were decreased after treatment with BAFF antagonist.[60] BAFF was increased in the serum of patients with SSc and correlated with the extent of skin fibrosis.[61] Addition of BAFF to co-cultures of B cells with SSc fibroblasts increased IL-6, TGFβ1 and collagen production.[21]

A randomized, double-blind, placebo-controlled, pilot trial assessed the efficacy of belimumab in early dcSSc patients treated with background MMF. There was significant improvement in skin fibrosis that was greater, although not statistically significant, in the group receiving MMF plus belimumab compared to MMF monotherapy.[62] Adverse effects of belimumab include increased risk of infections, while caution should be applied in patients with preexisting mood disorder.

1. **Tocilizumab.** Tocilizumab is a humanized monoclonal antibody against interleukin-6 receptor, administered intravenously or subcutaneously and is approved for the treatment of rheumatoid arthritis, systemic juvenile idiopathic arthritis and giant cell arteritis. IL-6 is increased in the peripheral blood and lesional skin from patients with SSc, and induces fibroblast collagen production.[63] IL-6 also induces Th17 differentiation and promotes B cell differentiation toward Ig-producing plasma cells.[64]

Case studies reported improvement in skin thickness,[65–67] however concern regarding gastrointestinal side effects was raised.[68] An observational study reported significant improvement in arthritis, with decrease in disease activity score based on 28 joint counts (DAS28) after 5 months of TCZ therapy.[69] A phase II study comparing tocilizumab (162 mg/week subcutaneously) vs placebo over 48 weeks followed by an open-label TCZ period to 96 weeks showed a trend towards skin score improvement.[70,71] Adverse effects of TCZ include increased risk of infections, elevation of liver enzymes, bone marrow suppression, elevation of lipids, and increased risk of gastrointestinal perforation in patients with diverticulitis.[64] TCZ should also be avoided in patients with preexisting or recent onset demyelinating disorder.

2. **Abatacept.** Abatacept is a recombinant CTLA4-Ig fusion protein that binds to CD80/CD86 on antigen-presenting cells, blocking CD28 binding to CD80/CD86 and consequently inhibiting T cell activation. In small case series, abatacept has shown good results regarding arthritis.[69] Skin thickening, both in patients with SSc and localized scleroderma, has also been improved with abatacept[72–74] and expression studies in skin biopsies showed modulation of genes implicated in inflammatory pathways.[72] Adverse effects of abatacept include increased risk of infections and – potentially serious – exacerbations of chronic obstructive pulmonary disease.
3. **Rituximab.** Rituximab (RTX) is a chimeric mouse/human monoclonal antibody, which binds specifically to the transmembrane antigen CD20, located in human pre-B and mature B lymphocytes. Skin biopsies from SSc patients showed increased skin infiltration of B cells in some patients.[75] B cells were also found in lung biopsies from patients with SSc-associated interstitial lung disease (ILD).[76] In scleroderma mouse models, B-cell depletion significantly improved skin fibrosis.[77] Many small studies evaluated the effect of rituximab in SSc. Among 20 relevant references found in the literature, 11 had less than ten patients and/or no comparison group. The remain 9 studies were: 1 open label RCT with two years follow up,[78,79] 1 open label comparative study,[80] 1 retrospective nested case-control study,[81] 1 double-blind RCT with 2 years follow-up,[82] 1 retrospective study in a single centre combined with literature review of published cases,[83] and 3 prospective open label studies.[84–86] The first study showed improvement in mRSS and lung function tests (FVC and DLCO)[78] and further improvement observed after two years of follow up.[79] The same results, of skin and lung function improvement, reported in the third study of 51 SSc patients with respiratory involvement.[80] Similarly, in the case – control nested study of 46 patients, mRSS were reduced in the RTX group, FVC stabilized and DLCO increased.[81] The second open label study assessed the skin score in progressive diffuse SSc[71] and other two in early disease.[84,86] Two of three studies described statistically significant improvements in mRSS from baseline with RTX at all time points[85,86] and the only trial with no significant changes in mRSS in RTX group was the other open label study.[84] The double-blind RCT study by Boonstra M et al. also examined 16 early (<2years disease duration) scleroderma patients.[82] Patients treated with Rituximab showed moderately

improvement, although not statistically significant, of lung function compared to patients on placebo. Skin score did not differ between groups.[82] On the contrary, Thiebaut M et al in their retrospective study of 53 patients (13 from a single centre in France combined with data from 40 additional patients retrieved from published cases) concluded that RTX improves skin, and lung function.[83] Currently RTX is considered in cases with worsening ILD following treatment with CyP. Adverse effects of Rituximab include increased risk for infections – including hepatitis B virus re-activation and herpes zoster – bone marrow suppression and potentially serious mucocutaneous reactions.

4. **Anti-TGF monoclonal antibody.** Transforming growth factor-β (TGF-β) is a growth factor with important homeostatic function in tissue repair processes, would healing, epithelial integrity and immune responses. Excessive TGF-β activity is associated with fibrosing disorders such as pulmonary fibrosis and SSc.[87] Mice with gain-of-function mutations in the TGF-β signaling pathway develop fibrosis in the skin and blood vessel walls in the lung and kidneys characteristic of SSc.[88] TGF-β expression in the lesional skin of SSc patients seems high in patients with severe and active disease, in contrast to established skin fibrosis.[89] There are also reports of upregulated expression of TGFβ receptors, such as integrins and thrombospondin-1, in skin fibroblasts suggesting that an autocrine TGF-β loop in SSc fibroblasts may be present.[90–92] TGFβ increases the expression of several pro-fibrotic genes in lung fibroblasts by inducing endothelin-1.[93] However, trials of the dual receptor endothelin-1 antagonist have not shown benefit.[94] Metelimumab, a human monoclonal neutralizing antibody to TGFβ, failed to improve skin fibrosis in 45 patients with early SSc.[95] Fresolimumab, a neutralizing antibody against all three TGFβ isoforms, was studied in an open label study in 15 SSc patients. Significant improvement in skin fibrosis was observed, while sequential skin biopsies showed that fresolimumab was efficient in blocking TGFβ activity. Adverse events included anaemia and bleeding.[96]

Emerging data on the use of biological drugs in the treatment of patients with SSc are summarized in Table 2.

B2.Synthetic targeted therapies

1. **Rapamycin**. Rapamycin, is a macrolide that binds to FK-506 binding protein 12 and inhibits the mammalian target of rapamycin and thus inhibits cytokine production, cell proliferation, and collagen production.[97,98] In a small single-blind study, 11 dcSSc patients of < 5 years duration were randomized to receive rapamycin (rapa) or MTX for 48 weeks. Rapamycin and MTX improved skin score, but FVC was declined in the rapa group.[99] Hypertriglycedemia was the most common adverse effect in the para group, whereas other adverse effects were comparable between the rapa and MTX groups.[99]
2. **Tyrosine kinase inhibitors**. Tyrosine kinases are small molecules involved in numerous intracellular processes, including in the production of PDGF and TGFβ production. Tyrosine kinase inhibitors (TKIs) have been used in malignancies and fibrotic disorders, while they've emerged as the next important breakthrough in the treatment of rheumatoid arthritis.[100] In SSc, imatinib, a first generation TKI, exhibited highly variable effects from un-effectivenes to clinical improvement in severe cases, but also considerable toxicity, including fluid retention, alopecia, anaemia, nausea, and diarrhea.[101-105] Second generation TKIs, nilotinib, and dasatinib, also have been evaluated in small, open-label studies. Nilotinib in patients with early dcSSc improved skin score at 12 months.[106] In a safety and pharmacokinetics study of 9 months duration, dasatinib improved skin score and stabilized lung function in few SSc patients.[107] The jury is still out for this class of drugs in SSc because of moderate therapeutic efficacy and serious toxicity.[26]

Response to treatment

As with most systemic multifaceted diseases, evaluation of treatment response in patients with SSc represents a difficult task. There is an increasing effort to identify biomarkers that are easy to measure in order to be able to assess disease progression and response to treatment in the clinic.[108] Currently, only cutaneous induration has been validated for diagnosis, prognosis or response to treatment in patients with SSc. Serum autoantibodies and nailfold capillaroscopic patterns are also used in

Table 2. Biologic drugs in the treatment of Systemic Sclerosis.

Drug	Mechanism of Action	Clinical Efficacy	*References*
IVIg	Blocks binding of - serum Ig, - B cell surface Ig, - T cell antigen receptors to their respective antigens	- improvement of skin score - improvement of hand function - reduction of joint pain	RCT: *58* Other: *56, 57*
Belimumab	human anti-BLyS mAb	- improvement in skin fibrosis (MMF as background medication)	RCT: *62*
Tocilizumab	humanized anti- IL-6 receptor mab	- improvement in skin thickness and arthritis	RCT: *70* Other: *65–69, 71*
Abatacept	recombinant CTLA4-Ig fusion protein Blocks T cell co-stimulation	- improvement in skin thickness - amelioration of arthritis	RCT: *72* Other: *69, 73, 74*
Rituximab	chimeric anti-CD20 mAb	- improvement of skin score - improvement or maintenance of lung function tests (FVC, DLCO)	RCT: *81, 82* Other: *79–81, 83, 84–86*
Fresolimumab	human anti TGFβ mab (neutralizes all 3 TGFβ isoforms)	- improvement in skin fibrosis	*96*

IVIg: Intravenous Immunoglobulin, RCT: Randomized Controlled Trial, mab: monoclonal antibody, BLyS: B Lymphocyte Stimulator, MMF: Mycophenolate Mofetil.

certain centers as tools to inform treatment decisions. Obviously, regular assessment of cardiopulmonary function (serial measurements of DLCO, FVC and pulmonary artery pressure among others) remain standard practice. However, substantial work has been done towards novel biomarkers. Gene expression patterns in the skin and other organs as well as gene expression changes associated with treatment response has been studied. Moreover it is speculated that potential biomarkers lie within extracellular vesicles (EVs). EVs enclose a vast array of macromolecules that are considered to mirror the physiological or pathological state of the cells of origin. Transcriptomic and proteomic analyses of EVs from SSc patients could provide a valuable source of novel biomarkers for the prognosis of our patients and their response to treatment.[108]

Concluding remarks

Therapeutic approach of patients with SSc should address all cardinal features of the disease and includes therapies for (a) the vascular manifestations, such as Raynaud's phenomenon, skin ulcers, pulmonary arterial hypertension (PAH) and scleroderma renal crisis, (b) fibrosis of the skin and internal organs as well as (c) immune cell dysregulation. Regarding vascular manifestations several agents have been established in every day practice: Angiotensing converting enzyme (ACE) inhibitors have changed the prognosis for renal crisis while endothelin-1 receptor antagonists, phosphodiesterase (PDE)-5 inhibitors, intravenous, and recently oral prostanoids have been approved for PAH. Fibrosis remains the most challenging part since no fibroblast directed therapy has been able to provide data that could lead to clinical use. On the other hand successful immunotherapy, especially when applied early in the disease course, is expected to prevent disease progression. Currently available immunotherapeutic agents for SSc were summarized here in. Real life data has proven that SSc is one of the most challenging and complex rheumatic diseases. Current treatment strategies are ineffective once fibrosis takes place. The future of SSc treatment we envision in the next few years will most probably include early introduction of medications directed against molecules involved in immune cells-fibroblasts communication.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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