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Review article

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Emerging therapies for the treatment of systemic sclerosis

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Abstract

Systemic sclerosis (SSc) is an autoimmune disease in which fibrotic, vascular, autoimmune and fibrotic mechanisms synergize to promote disease progression. SSc is associated with high morbidity and mortality, primarily owing to fibrotic tissue remodelling and subsequent organ failure. Despite progress with the approval of novel therapies, mortality remains high; approximately half of the people diagnosed with SSc will succumb to disease. This statistic highlights the considerable need for novel, effective therapies. Indeed, SSc has become a disease with very active drug development. Numerous drugs with different modes of actions are currently evaluated in or are about to enter clinical trials in SSc. These clinical trials provide hope for effectively slowing or even halting the progression of fibrosis and thereby further improving outcomes for patients with SSc.

Sections

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Key points

- Currently available drugs for systemic sclerosis (SSc) might slow down disease progression, but do not halt it, generating a great medical need for novel, more effective therapies.
- These drug candidates have a broad-spectrum of distinct anti-inflammatory and/or anti-fibrotic modes of action relevant to the pathogenesis of SSc.
- A large number of drug candidates and cellular therapies with different molecular modes of actions are currently under investigation or about to enter clinical trials in SSc.

Introduction

Systemic sclerosis (SSc) is a connective tissue disease that is histopathologically characterized by vasculopathy, autoimmunity and fibrotic tissue remodelling[1]. Approximately 50% of people diagnosed with SSc will eventually die as a direct consequence of disease, which represents the highest disease-related mortality of all autoimmune rheumatic diseases[2]. Thus, novel, effective therapies for the treatment of SSc are required. Owing to this need, the development of therapies to treat SSc has become an active area of research. The interest of pharmaceutical companies in SSc has also been stimulated by several positive randomized controlled trials (RCTs) with nintedanib, tocilizumab and rituximab, which have been published within the past 5 years (Table 1). These new drugs greatly augment the evidence-based therapeutic arsenal for the treatment of the fibrotic manifestations of SSc, which were previously limited to mycophenolate mofetil, cyclophosphamide, haematopoietic stem cell transplantation (HSCT) after high-dose chemotherapy and, eventually, methotrexate (for skin fibrosis only).

However, despite this progress, the need for more effective therapies for the treatment of SSc remains high. Treatments that are currently available, perhaps with the exception of HSCT after high-dose chemotherapy, only slow down progression of fibrotic tissue remodelling, but do not halt it or even induce regression of fibrotic damage for most patients[3]. Moreover, most of the primary outcomes of previous and ongoing clinical trials mainly focus on interstitial lung disease (ILD) and, to a lesser extent, on skin fibrosis. There is a lack of evidence from RCTs on how to treat other common and life-threatening fibrotic manifestations of SSc, such as primary myocardial involvement or intestinal involvement.

In this Review, we provide an overview of the drugs and cellular therapies that are currently being evaluated in clinical trials for the treatment of SSc (Table 2). We discuss their mode-of-action and the preclinical data for each approach.

Fibroblast targeting approaches

Fibroblasts are key effector cells involved in fibrotic remodelling. They are not only the main source of extracellular matrix deposition in fibrotic tissues but may also modulate inflammatory processes and vascular remodelling.

Targeting hedgehog signalling

Numerous studies show that hedgehog signalling is implicated in fibrotic tissue remodelling in a variety of fibrotic disorders, including SSc[4–12]. Hedgehog signalling is essential to organ development. During homeostasis, the activity of this signalling pathway is very low in the majority of cells and tissues, except for stem cells, in which hedgehog signalling has an important role in the regulation of behaviour and function. Nevertheless, during fibrotic tissue remodelling, hedgehog signalling is activated and has pathogenic effects[12–14]. The expression of sonic hedgehog (SHH, which is a key hedgehog ligand in the context of skin fibrosis) and of GLI1 and GLI2 (hedgehog signalling-associated transcription factors) are upregulated in the skin of patients with SSc[6,15]. In addition, the SHH levels in the serum of patients with SSc are increased compared with healthy individuals and correlate with fibrotic burden[16]. Hedgehog signalling is highly interlinked with other pathways that are implicated in fibrotic tissue remodelling; for example, the activation of hedgehog signalling in SSc is caused, in part, by TGFβ, which not only induces the expression of SHH but also activates the promoter of *GLI2* to upregulate GLI2 expression in fibroblasts[6]. Hedgehog signalling also stimulates fibroblasts to differentiate into myofibroblasts and induces skin fibrosis[6]. Pharmacological or genetic inactivation of hedgehog signalling ameliorates fibrosis in a wide variety of mouse models of fibrosis and in many different organs[17–20].

The inhibition of hedgehog signalling is currently being evaluated for its anti-fibrotic effects in pulmonary fibrosis. Current pharmacological efforts to target hedgehog signalling focus on small molecule inhibitors of Smoothend (SMO). SMO is a G protein coupled receptor that activates GLI transcription factors in response to hedgehog ligand–receptor binding (these ligands include SHH, Indian hedgehog and desert hedgehog). Two SMO inhibitors, sonidegib and vismodegib, have been approved by the FDA for the treatment of basal cell carcinoma[21]. In a phase IIa RCT of patients with idiopathic pulmonary fibrosis (IPF), individuals receiving the SMO inhibitor ENV-101 (200 mg daily) were found to have a significantly higher predicted FVC mean change from baseline after 12 weeks than those receiving placebo (1.9% increase in the ENV-101 arm versus 1.3% decrease in the placebo arm)[22]. Although further studies with more patients and longer follow-up are required to confirm these results, the increase in FVC upon ENV-101 treatment might be indicative of anti-fibrotic remodelling induced by SMO inhibition. Indeed, preclinical findings demonstrate that inhibition of hedgehog signalling can deactivate myofibroblasts and induce re-differentiation into resting fibroblasts[4]. A confirmatory phase IIb trial of ENV-101 in IPF is currently recruiting (NCT06422884).

Targeting LPAR1 signalling

Fipaxalparant is a small molecule inhibitor that inhibits lysophosphatidic acid receptor 1 (LPAR1). This inhibitor blocks the effects of phospholipid lysophosphatidic acid (LPA)[23]. LPA is a small molecule mediator that is released during enzymatic breakdown of lipid membranes by the enzyme autotaxin. LPA is part of the tissue injury response that can promote inflammation and scarring and evidence suggests that LPA is a mediator of bleomycin-induced lung fibrosis[24]. LPA signals through a family of receptors (LPAR1–LPAR6), which are expressed on a variety of cells that contribute to the pathogenesis of SSc. LPAR1 is considered the dominant LPA receptor in the pathogenesis of fibrotic tissue remodelling. Clinical trials of LPAR antagonists in IPF have shown positive results[25]. A small phase IIa trial of an LPAR1 antagonist in diffuse cutaneous SSc (dcSSc) demonstrated that treatment with this antagonist attenuated LPA-regulated target genes in vivo and showed a beneficial trend in modified Rodnan Skin Score (mRSS) over 12 weeks compared with placebo[26]. This trial led to a larger randomized controlled phase IIb study (BEACON), which did not reach its primary end point of changes in FVC (NCT04781543).

Table 1 | Clinical trials with positive primary or secondary outcomes that changed the management of SSc

Drug	Molecular target	Clinical trial	Target population	Clinical trial design	Primary outcome	Key secondary outcomes
Nintedanib	Multiple tyrosine kinases	SENCSIS[184]	SSc-ILD	Phase III placebo-controlled RCT	Adjusted annual rate of change in FVC	Change in mRSS at 52 weeks
Nintedanib	Multiple tyrosine kinases	INBUILD[185]	PPF including SSc	Phase III placebo-controlled umbrella RCT	Adjusted annual rate of change in FVC	Change in total score on K-BILD questionnaire at 52 weeks
Tocilizumab	IL-6 receptor	faSScinate[186]	Early inflammatory dcSSc	Phase II placebo-controlled RCT	Change in mRSS at 24 weeks	Change in FVC at 48 weeks
Tocilizumab	IL-6 receptor	FocuSSed[187]	Early inflammatory dcSSc	Phase III placebo-controlled RCT	Change in mRSS at 48 weeks	Change in FVC at 48 weeks
Rituximab	CD20	DESIRES[188]	SSc	Investigator-initiated phase II placebo-controlled RCT	Change in mRSS at 24 weeks	Change in FVC at 24 weeks
Rituximab	CD20	RECITAL[189]	Severe or progressive CTD including SSc	Phase IIb, double-blind, double-dummy RCT	Change in FVC at 24 weeks	Change in FVC at 48 weeks

CTD, connective tissue disease; dcSSc, diffuse-cutaneous SSc; FVC, forced vital capacity; ILD, interstitial lung disease; K-BILD questionnaire, King's Brief Interstitial Lung Disease questionnaire; mRSS, modified Rodnan Skin Score; PPF, progressive pulmonary fibrosis; RCT, randomized control trial; SSc, systemic sclerosis.

Other approaches that target LPA signalling, such as autotaxin inhibition, have also been investigated. Ziritaxestat, an autotaxin inhibitor, was evaluated in IPF and in SSc with positive results for mRSS in a small phase IIa study[27]. However, parallel trials in IPF reported safety concerns and a lack of efficacy, and increased mortality was reported in the group receiving the highest dose in the ISABELA trials[28], which led to the clinical development of ziritaxestat being discontinued. Based on these results, targeting LPA signalling in SSc is currently considered challenging.

Anti-TGFβ3 antibodies

The regulation of tissue repair and development pathways by members of the TGFβ family is well established. TGFβ has three major isoforms (TGFβ1, TGFβ2 and TGFβ3) that signal through the same receptor complex[29]. Although the downstream canonical and non-canonical signalling pathways are shared, these isoforms differ in their bioavailability, accessory protein binding and cell and tissue-specific expression patterns[30]. TGFβ ligands are generally complexed to latent TGFβ binding proteins and are released from sequestered, inactive forms bound to matricellular proteins in response to conformational changes of integrins[31]. All three TGFβ isoforms seem to be profibrotic in preclinical models and findings suggest that attenuating TGFβ signalling can prevent or even reverse fibrosis in preclinical models[1,32]. Ample evidence indicates that TGFβ pathways are upregulated in many fibrotic diseases, including SSc. The first study of TGFβ inhibition in SSc evaluated the monoclonal antibody CAT-192 (metelimumab), which binds to TGFβ1 (ref. 33). Although this phase I–II trial showed some positive dose-dependent changes in mRSS at 6 months, these changes did not reach statistical significance. In addition, biomarker studies in this trial were limited and it remains unclear if in vivo antagonism of TGFβ signalling pathways occurred[33].

Other approaches involve targeting TGFβ ligands. An uncontrolled trial of fresolimumab in SSc showed encouraging molecular benefits; the target genes *COMP* and *TSP1* were downregulated and a two-gene score, proposed as a biomarker for the progression of skin fibrosis, improved[34]. However, there were concerns about toxicity including gastrointestinal tract effects, vascular lesions and a possible increase in the incidence of proliferative lesions of the skin (keratoacanthomas). The TGFβ1/3 ligand trap, AVID200, has been evaluated in SSc and in myelofibrosis[35]; however, these studies were too small and/or lacked placebo arms to definitively test the hypothesis of blocking TGFβ ligands as an anti-fibrotic approach in SSc. Determining lack of efficacy or unacceptable toxicity is crucial as the TGFβ pathway remains one of the most relevant targets for SSc owing to extensive preclinical evidence. The emergence of the activin signalling inhibitor, sotatercept, as an approved therapy for pulmonary arterial hypertension (PAH), including PAH associated with connective tissue disease, with remarkable benefit in clinical trials, confirms the feasibility of targeting TGFβ superfamily members and serves as a reminder that these pathways are closely interdependent and so targeting one member might affect signalling by others[36].

Currently, there is an ongoing phase Ib dose ranging trial of RG-6315 (RO-7303509), a human monoclonal antibody that targets TGFβ3, in SSc (NCT05462522)[37]. RG-6315 is administered via subcutaneous or intravenous routes and is a novel molecular entity. It is hypothesized that TGFβ3 might be an important profibrotic mediator and that neutralization could have fewer adverse effects than targeting all TGFβ ligands, TGFβ1 or TGFβ2 (ref. 32). Conversely, historical literature supports TGFβ3 having anti-fibrotic effects based on evidence from non-scarring fetal wound healing in animal models[38]. This finding was not substantiated in clinical trials and thus clinical development of recombinant TGFβ3 as a potential anti-fibrotic therapy has ceased.

Dual targeting of fibroblasts and immune cells

Several emerging therapeutic approaches target fibroblasts directly and indirectly by modulating inflammatory immune responses.

Targeting phosphodiesterase 4b

Phosphodiesterases (PDEs) are a large group of enzymes comprising 11 subfamilies with diverse functions. Members of the PDE4 subfamily (PDE4A, PDE4B, PDE4C and PDE4D) are the major subfamily of PDEs expressed in immune cells[39]. PDE4s regulate cytokine synthesis and other pro-inflammatory pathways in leukocytes via hydrolysis of cyclic AMP[40]. Indeed, non-selective PDE4 inhibitors are in clinical use for the treatment of inflammatory diseases; apremilast is approved for plaque psoriasis, psoriatic arthritis and Behçet syndrome, and

Table 2 | Therapies currently in or about to enter clinical trials in SSc

Therapy	Entity	Molecular target(s)	Predominantly targeted mechanism(s)	Predominant target cell(s)	Developmental stage
ENV-101	Small molecule	Smoothend	Hedgehog signalling	Fibroblast activation	Phase II trial, recruiting
Fipaxalparant	Small molecule	LPAR1	LPA signalling	Fibroblast activation	Phase IIb trial, completed
Ziritaxestat	Small molecule	Autotaxin	LPA signalling	Fibroblast activation	Phase II trial, terminated
RG6315 (RO-7303509)	Antibody	TGFβ3	TGFβ signalling	Fibroblast activation	Phase II trial, active
Nerandomilast	Small molecule	PDE4B	cAMP signalling	Immune cell and fibroblast activation	Phase III trial in progressive pulmonary fibrosis, completed; phase IIb trial in SSc, in preparation
CAN10	Antibody	IL1RAP	IL-1, IL-33 and IL-36 signalling	Immune cell and fibroblast activation	Clinical trial in preparation
Dersimelagon (MT-7117)	Small molecule	MC1R	αMSH–MC1R signalling	Immune cell and fibroblast activation	Phase II trial, completed
Asengeprast	Small molecule	GPR68	GPR68 signalling	Immune cell and fibroblast activation	Phase IIa trial completed; phase IIb trial, in preparation
CAL101	Antibody	S100A4	S100A4 signalling	Immune cell and fibroblast activation	Clinical trial in preparation
Itacitinib	Small molecule	JAK1	JAK1–STAT signalling	Immune cell and fibroblast activation	Phase II investigator-initiated trial, ongoing
Vixarelimab	Antibody	OSM	OSM signalling	Immune cell and fibroblast activation	Phase II trial, recruiting
Nemolizumab	Antibody	IL-31RA	IL-31 signalling	Immune cell and fibroblast activation	Phase II trial, completed
Efgartigimod	Antibody	Neonatal Fc receptor	Reduction of autoantibody titres	Autoantibodies	Phase II trial, recruiting
Belimumab	Antibody	BAFF	BAFF signalling	B cells	Phase II–III trial, recruiting
Ianalumab	Antibody	BAFF receptor	BAFF signalling	B cells	Phase II trial, recruiting
Telitacicept	Decoy receptor	BAFF	BAFF signalling	B cells	Phase II IIT trial, recruiting
Inebilizumab	Antibody	CD19	B cell depletion	B cells	Phase IIa trial, completed
Anti-CD19 CAR T cells	CAR T cell	CD19	Deep depletion of B cells	B cells	Several phase II trials recruiting or in preparation
Anti-BCMA CAR T cells	CAR T cell	BCMA	Deep depletion of B cells including plasma cells	B cells and plasma cells	Phase II trials, in preparation
CD19xCD3, CD20xCD3 and BCMAxCD3 BiTEs	BiTEs	CD19, CD20 and BCMA	Deep depletion of B cells including plasma cells	B cells and plasma cells	Several phase I and phase IIa trials, in preparation
Amlitelimab	Antibody	OX40 ligand	T cell proliferation, survival, and context-dependent T_H1, T_H2, and T_H9 cell skewing, T_{FH} cell development and B cell help	T cells and B cells	Phase II trial, recruiting
Tulisokibart	Antibody	TL1A	TL1A–DR3 signalling	T cells and ILCs	Phase II trial, recruiting
Brodalumab	Antibody	IL-17A	IL-17 signalling	T_H17 cells	Phase II trial, completed (results withdrawn)
Guselkumab	Antibody	p19	IL-23 signalling	T_H17 cells	Phase II trial, completed
Tibulizumab	Bispecific antibody	IL-17A and BAFF	IL-17 and BAFF signalling	T_H17 cells and B cells	Phase II trial, recruiting

Table 2 (continued) | Therapies currently in or about to enter clinical trials in SSc

Therapy	Entity	Molecular target(s)	Predominantly targeted mechanism(s)	Predominant target cell(s)	Developmental stage
Anifrolumab	Antibody	IFNAR1	Type I interferon signalling	Multiple target cells	Phase III trial, recruiting
Efzofitimod	HARS–IgG fusion protein	Neuropilin-2	HARS–neuropilin-2 signalling	Macrophages and other immune cells	Phase II trial, recruiting
Avenciguat	Small molecule	sGC	cGMP signalling	Broad spectrum including fibroblasts, vascular cells and possibly immune cells	Phase II trial, recruiting
Ifetroban	Small molecule	TPR	Thromboxane–prostanoid signalling	Broad spectrum including fibroblasts and vascular cells	Phase II trial, recruiting

αMSH, α-melanocyte-stimulating hormone; BAFF, B cell activating factor; BCMA, B cell maturation antigen; BiTEs, bispecific T cell engagers; cAMP, cyclic adenosine monophosphate; CAR, chimeric antigen receptors; cGMP, cyclic guanosine monophosphate; DR3, death receptor 3; HARS, histidyl-tRNA synthetase 1; IFNAR1, interferon-α/β receptor subunit 1; IL-31RA, IL-31 receptor A; IL1RAP, IL-1 receptor associated protein 1; ILCs, innate lymphoid cells; JAK1, Janus kinase 1; LPA, lysophosphatidic acid; LPAR1, lysophosphatidic acid receptor 1; MC1R, melanocortin receptor 1; OSM, oncostatin M; PDE4B, phosphodiesterase 4B; sGC, soluble guanylate cyclase; SSc, systemic sclerosis; STAT, signal transducer and activator of transcription; T_{FH} cell, T follicular helper cell; T_H cell, T helper cell; TL1A, TNF-like ligand 1A; TPR, thromboxane prostanoid receptor.

roflumilast is approved for chronic obstructive pulmonary disease. However, the systemic adverse effects, particularly gastrointestinal effects, of inhibiting PDE4 limit its use[41,42], particularly the use of higher doses that provide a more effective inhibition of PDE4 activity. The PDE4B subtype exhibits variant-specific expression patterns with high levels of expression in immune cells and tissue-resident cells in the lungs, but lower levels in the intestinal tissues[43]. Thus, selective inhibition of the PDE4B subtype might reduce the risk of gastrointestinal adverse events and enable higher doses to be used for more effective targeting of PDE4B activity. Nerandomilast is a PDE4 inhibitor that preferentially inhibits PDE4B with a 9-fold selectivity over other PDE4 subtypes[44]. In vitro, nerandomilast skews the balance from a pro-inflammatory to an anti-inflammatory cytokine profile, inhibits fibroblast proliferation and reduces myofibroblast differentiation and collagen synthesis[44]. Moreover, nerandomilast ameliorates experimental bleomycin-induced dermal and pulmonary fibrosis[45]. Of particular interest, nerandomilast prevented the decline of FVC over 12 weeks compared with placebo in a proof-of-concept phase II trial in patients with IPF[46]. A follow-up phase III RCT of nerandomilast in patients with progressive pulmonary fibrosis other than IPF met its primary end point of reduced decline in FVC and also showed reduced mortality in the nerandomilast arm compared with standard of care[47]. However, in this trial, patients were not treated according to current rheumatology standards; patients received less background therapy than would be expected for progressive disease. Nerandomilast is currently being evaluated in SSc in a phase IIb platform trial using the CONQUEST platform[48]. CONQUEST is the first platform clinical trial in the field of rheumatology, in which multiple investigational drugs can be evaluated in parallel with a shared placebo group. In this trial, changes in FVC are the primary end points and changes in mRSS are amongst the secondary endpoints.

Anti-IL1RAP antibodies

IL-1, IL-33 and IL-36 are pro-inflammatory cytokines that are linked to the aetiology of fibrotic tissue remodelling[49]. The protein levels of IL-1β, IL-33 and IL-36γ are upregulated in the skin of patients with SSc compared with healthy donors, expression of the respective receptors for these cytokines were also upregulated on relevant target cells such as fibroblasts, endothelial cells and leukocytes[50]. Bioinformatic modelling using gene expression datasets from mice that lack each of these individual cytokines and SSc skin provided evidence that all three cytokines can regulate specific, and only partially overlapping, sets of genes that are differentially expressed in SSc skin[50], which provides evidence that IL-1, IL-33 and IL-36 synergistically drive the pathogenesis of SSc. All three cytokines might be blocked simultaneously by targeting the IL-1 receptor accessory protein (IL1RAP). IL1RAP is an essential co-receptor for the IL-1 receptor, the IL-33 receptor (also known as ST2) and the IL-36 receptor and is required for downstream signalling of these cytokine receptors[51]. IL1RAP is overexpressed in SSc skin compared with healthy skin and the messenger RNA (mRNA) levels of several molecules associated with IL1RAP signalling are increased in SSc skin[50]. Blocking IL1RAP with a monoclonal antibody (mCAN10) in mice interfered with the activation of a transcriptional regulatory network of genes that are implicated in inflammation and fibrosis and also ameliorated experimental dermal and pulmonary fibrosis in three different mouse models of SSc[50]. A first-in-human phase I clinical study of a humanized anti-IL1RAP antibody (CAN10) demonstrated good tolerability and successful target engagement (NCT0614337)[50]; a phase II study in SSc is currently in preparation.

Activation of MC1R signalling

The melanocortin receptors (MCRs) are a family of G protein-coupled receptors that consists of five members with different functions. MC1R is not only expressed on melanocytes, but also on other cell types such as fibroblasts, monocytes, endothelial cells and keratinocytes, with comparable expression patterns in SSc and healthy skin[52].

Although MC1R is best known for its involvement in melanin production in melanocytes via α-melanocyte-stimulating hormone (αMSH) binding, activation of MC1R also mediates anti-inflammatory effects that include inhibition of nuclear factor-κB (NF-κB) and shifts in the balance from pro-inflammatory to anti-inflammatory mediators with suppression; MC1R suppresses TNF, IL-1, IL-6, IL-8, prostaglandin E2, IFNγ and adhesion molecules and induces the expression of IL-10 (ref. 53).

The first direct evidence of a role for MC1R in fibrotic tissue remodelling was that αMSH, the MC1R ligand, suppresses bleomycin-induced skin fibrosis in mice; mice that lack MC1R signalling have exacerbated skin fibrosis[54]. Treatment with dersimelagon phosphoric acid

(MT-7117), an orally bioavailable agonist for MC1R that is selective for MC1R over other MCRs, also ameliorated bleomycin-induced inflammation and fibrosis of the skin. Incubating human dermal fibroblasts with MT-7117 inhibited TGFβ-induced *ACTA2* expression, which demonstrates a direct effect on fibroblasts in addition to anti-inflammatory effects[52]. Activation of MC1R by αMSH binding also ameliorates vascular dysfunction in lipopolysaccharide-induced cutaneous vasculitis[55] and ischaemia–reperfusion models[56]; however, whether these findings are relevant for SSc-associated vasculopathy remains to be studied in relevant models.

A randomized, placebo-controlled phase II clinical trial of MT-7117 in patients with dcSSc, with a change in American College of Rheumatology (ACR)–Composite Response Index in Systemic Sclerosis (CRISS) at 52 weeks being the primary end point, showed no difference between patients treated with MT-7117 and placebo[57].

GPR68 inhibition

GPR68 is a proton-sensing G protein coupled receptor that is widely expressed on many cell types[58]. It has emerged as a sensor of the pH in the cellular microenvironment that is activated by the release of protons at sites of tissue damage. GPR68 is implicated in tumour growth regulation and was identified in a variety of tumours as a suppressor of progression and metastasis[59]. The drug asengeprast (FT011) was developed as a derivative of tranilast and preclinical assays indicate that this drug could be an anti-fibrotic agent[60]. In a small phase IIa clinical trial of FT011 in SSc, treatment was associated with an improved ACR–CRISS score (NCT04647890). Treatment with asengeprast for 12 weeks (but not placebo) demonstrated inhibitory effects on a marker gene set linked to renal fibrosis that is also enriched in SSc skin; however, this trial was limited by the imbalanced background immunosuppression across treatment arms, the short duration of the study and the small number of participants. Previous studies have shown similar beneficial effects for potential therapies at phase II that were not observed in phase III trials (such as lenabasum)[61]. A further phase IIb study of asengeprast in SSc is planned.

Targeting S100A4

As previously discussed, targeting damage response signalling is emerging as a novel approach for the treatment of SSc and other inflammatory and fibrotic diseases. A strategy that has considerable preclinical support but has not yet been tested in human disease is targeting the damage-associated molecular pattern (DAMP) protein S100A4. The S100 proteins are a large family defined by solubility characteristics. S100A4 is released by damaged cells and can function both intracellularly and extracellularly to promote inflammation and fibrosis[62]. Notably, S100A4 has been identified as the fibroblast marker FSP-1, which was first identified in cells undergoing epithelial-mesenchymal transition[63]. Evidence indicates that functional interaction occurs between S100A4 and TGFβ pathways[64], and that this protein can activate cells directly through engagement of cell-surface receptors including Toll-like receptor 4 (ref. 65) and the receptor for advanced glycation end products[66]. Mice lacking S100A4 are protected from experimental dermal and pulmonary fibrosis[64]. In addition, neutralizing antibodies against S100A4 can attenuate pre-established bleomycin-induced skin fibrosis and induce its regression in mice[67]. In humans, S100A4 is increased in the serum of people with SSc compared with healthy individuals, with highest levels found in those with severe disease and lung fibrosis[68]. Treating cultured SSc fibroblasts or precision cut skin slices from people with SSc with the neutralizing anti-S100A4 antibody CAL101 reduced SSc-specific transcriptional signatures[68,69]. A phase I clinical trial of this antibody was completed in 2024 and was well tolerated, with no serious adverse events reported across all tested doses (J.H.W.D., unpublished observations). Future studies to evaluate the therapeutic potential, safety and pharmacokinetics of CAL101 in fibrotic diseases such as SSc are currently in preparation.

Targeting JAK–STAT3 signalling

Growing evidence supports aberrant activation of Janus kinase (JAK)–signal transducer and activator of transcription (STAT) signalling in SSc. JAK1 and JAK2 are increasingly phosphorylated and thereby activated in the skin of patients with SSc and accumulate in immune cells and fibroblasts[70–75]. JAKs synergize with other kinases such as SMAD3, JNK, SRC and c-ABL to activate STAT3 (ref. 72). In addition to STAT3, a genetic polymorphism of the *STAT4* gene was found to be associated with dcSSc and might promote fibrotic tissue remodelling in mice[76,77]. Pharmacological or genetic inactivation of JAK1, JAK2 or STAT3 inhibited fibroblast-to-myofibroblast differentiation and experimental dermal and pulmonary fibrosis[70–75]. These findings prompted an investigator-initiated clinical trial with the selective JAK1 inhibitor itacitinib in France, which is currently recruiting (NCT04789850).

Anti-OSM and IL-31RA antibodies

The oncostatin M receptor (OSMR, also known as oncostatin M-specific receptor subunit β) is a member of the type I cytokine receptor family. OSMR heterodimerizes with gp130 (also known as interleukin 6 signal transducer) to form the type II OSMR with the IL-31 receptor A (IL-31RA) to form the IL-31 receptor. OSMR thus transduces oncostatin M (OSM) and IL-31-induced signalling events. Two different antibodies that target these signalling cascades have entered clinical trials in SSc, vixarelimab and nemolizumab. Vixarelimab is a recombinant human monoclonal antibody that targets OSMR and has shown efficacy in a phase IIa clinical trial in the skin condition prurigo nodularis[78]. Nemolizumab is a recombinant humanized monoclonal antibody that targets IL-31RA and has also shown efficacy in a phase III clinical trial in prurigo nodularis[79]. These findings are in keeping with the known role of IL-31 in pruritus[80]. IL-31 has also been identified as a potential mediator in SSc; IL-31 expression is upregulated in the skin of patients with SSc and is found in dermal blister fluid[81]. Moreover, IL-31 directly promotes collagen production in dermal fibroblasts and indirectly by enhancing T helper 2 (T_H2) immune responses[82]. The levels of OSM are also increased in the blood of patients with SSc[83,84]; however, a 2022 phase I study of an anti-OSM monoclonal antibody (GSK2330811) in SSc showed no differences between treatment and placebo groups and no favourable clinical or biomarker outcomes[85]. Importantly, there was also a clear signal of toxicity with anaemia and thrombocytopenia. These adverse effects probably reflect 'on target' toxicity related to the role of OSM in haematopoiesis. These findings make OSM an unlikely target for future clinical development in SSc; however, there is plausible evidence supporting the potential role of OSM in the pathogenesis of SSc[86] and so if vixarelimab can achieve inhibition without toxicity and have additional anti-fibrotic benefits via its action on IL-31 pathways these effects might justify further evaluation of targeting OSM in SSc. This rationale underlies the ongoing evaluation of vixarelimab in a two-cohort, phase II, multicentre, randomized, double-blind, placebo-controlled study in patients with IPF and in patients with SSc-associated ILD (SSc-ILD) (NCT05785624). In addition, a phase II, open-label clinical trial of nemolizumab was conducted in patients with SSc, but the results remain unpublished (NCT05214794).

Targeting B cells and autoantibodies

Emerging evidence suggests that B cells are key effector cells in SSc. Thus, several approaches to targeting B cells or B cell-related mechanisms are currently being evaluated for the treatment of SSc.

Fc receptor blockade

Studies in mice indicate that the neonatal Fc receptor (FcRn) transports IgG from the milk of nursing dams to pups[87] and regulates IgG turnover in adult mice[88]. FcRn extends the half-life of IgG by reducing its lysosomal degradation[89–91]. IgG and other serum proteins are continuously internalized into cells through pinocytosis with subsequent lysosomal degradation. FcRn binds IgG (and other serum proteins) at the acidic pH within early endosomes, and releases it back into the circulation, as FcRn cannot bind IgG at the neutral pH of the extracellular environment[92,93]. Of interest for the pathogenesis of SSc, the expression of FcRn is regulated by pro-inflammatory cytokines; TNF induces the expression of FcRn, whereas IFNγ downregulates FcRn expression[94].

The antibody fragment efgartigimod alfa is a first-in-class drug that interferes with FcRn-induced recycling of IgG. Treatment with efgartigimod alfa decreases the level of circulating IgG by up to 75%, with maximal effects observed within 4 weeks, with corresponding decreases in autoantibody levels in humans[95]. In addition, the simultaneous inhibition of albumin recycling did not lead to significant changes in serum albumin levels[95]. Efgartigimod alfa demonstrated efficacy for the treatment of myasthenia gravis and is approved for the treatment of generalized anti-acetylcholine receptor antibody-positive myasthenia gravis by the FDA and EMA. Based on its mode of action, efgartigimod alfa is currently under investigation for a variety of different autoimmune diseases, including SSc. A multicentre, randomized, placebo-controlled, double-blinded, phase II trial with a 2:1 randomization of efgartigimod versus placebo and changes in mRSS after 48 weeks as the primary outcome is currently recruiting (NCT06655155).

BAFF inhibition

B cell activating factor (BAFF, also known as B lymphocyte stimulator) is a crucial cytokine in B cell homeostasis, survival and differentiation. Dysregulation of BAFF has been implicated in various autoimmune diseases, including SSc. Considerable experimental evidence indicates that BAFF has a profibrotic role. Culturing dermal fibroblasts with peripheral blood B cells from patients with SSc demonstrated that BAFF stimulates cell-contact-induced release of profibrotic mediators, such as IL-6, CCL2 and TGFβ1, as well as collagen gene expression from fibroblasts[96]. Moreover, genetic ablation of BAFF or BAFF neutralization attenuated fibrotic tissue remodelling in the Tsk/$^{+}$ mouse model of skin fibrosis and in a bleomycin-induced lung fibrosis mouse model[97,98]. In people with SSc, *BAFF* gene expression levels correlate with the upregulation of a type I interferon signature and serum type III procollagen N-terminal propeptide levels, which suggests a potential link between innate and adaptive immune responses via BAFF[99]. Finally, BAFF promotes the survival and activation of autoreactive B cells, which leads to autoantibody production. As BAFF has a crucial role in B cell hyperactivation, autoimmunity and fibrosis in SSc, agents that block BAFF are being explored as potential therapeutic strategies for SSc.

Two antibodies, belimumab and ianalumab, which target aberrant BAFF signalling are currently being evaluated in clinical trials in SSc. Belimumab is a fully human monoclonal antibody that neutralizes BAFF and is approved for the treatment of moderate-to-severe systemic lupus erythematosus (SLE) and lupus nephritis. The efficacy and safety of belimumab in patients with dcSSc and ILD is currently being investigated in a phase II–III, randomized, double-blind, placebo-controlled trial (NCT05878717). Ianalumab (VAY-736) is a fully human monoclonal antibody that targets the BAFF receptor and has a dual mechanism of action as it not only blocks BAFF–BAFF receptor interactions but also depletes B cells by antibody-dependent cellular cytotoxicity. Ianalumab has shown favourable safety and encouraging efficacy in SLE and Sjögren disease, and is being evaluated in an ongoing phase II, randomized, double-blind, placebo-controlled trial in patients with SSc (NCT06470048).

Telitacicept is a fully human fusion protein composed of the transmembrane activator and CAML interactor (TACI; also known as TNFRSF13B) and IgG1. Telitacicept is a soluble decoy receptor for BAFF and APRIL that can inhibit the maturation of immature B cells and the differentiation of mature B cells into plasma cells by blocking BAFF and APRIL, respectively[100]. An investigator-initiated trial of telitacicept in SSc is currently recruiting in China (NCT06546540).

Novel B cell-targeted approaches

Several novel approaches that target antigens on specific B cell populations are currently under investigation. The target antigens CD19, CD20 and B cell maturation antigen (BCMA) are expressed during different stages of B cell development. CD20 is induced in pre-B cells and expressed on immature, naive, germinal centre and memory B cells and on a subset of plasmablasts, whereas plasma cells do not express CD20. CD19 is expressed throughout B cell development from pro-B cells to fully differentiated B cells; however, only a subset of plasma cells expresses CD19 and the plasma cell compartment is thus only partially targeted by therapeutics that target CD19. BCMA is expressed at the later stages of B cell development with induction on germinal centre B cells, and expression on all memory B cells, plasmablasts and plasma cells; BCMA thus offers the opportunity to target all antibody-producing B cells[101].

Despite most of the evidence thus far being from case reports and case series from single centres, autologous anti-CD19 chimeric antigen receptor (CAR) T cells show clinical efficacy and relative safety in the treatment of SSc and other autoimmune diseases[102–104]. The available data provide evidence of major efficacy in a population of patients with progressive SSc previously refractory to multiple treatments. Reported beneficial effects include regression or at least stabilization of fibrotic manifestations (such as dermal, pulmonary and cardiac fibrosis), rapid regression of inflammatory manifestations (such as arthritis or myositis) and improved microcirculation with reduced frequency and intensity of Raynaud attacks and lower incidence of fingertip ulcers[105]. Early evidence suggests that treatment with anti-CD19 CAR T cells might be better tolerated than high-dose chemotherapy followed by autologous HSCT and that this treatment is safe and effective in patients with SSc and advanced pulmonary or cardiac involvement, who are no longer eligible for HSCT (J.H.W.D., unpublished observations). Additional unpublished evidence indicates that anti-CD19 CAT T cell therapy, but not the anti-CD20 antibody rituximab, can restore the papillae in the upper dermis, which are typically flattened in SSc (J.H.W.D., unpublished observations). Although further histological studies and molecular analyses are required to support these initial findings, they indicate that anti-CD19 CAR T cell therapies not only halt disease progression but can also induce, at least to some extent, the regeneration of fibrotic skin, which could possibly extend to fibrosis in other organs. CD19-positive cells are rapidly depleted in peripheral blood, but also in lymph nodes following anti-CD19 CAR T cell therapy,

which is associated with strongly decreased levels or even complete loss of disease-associated autoantibodies[106]. The persistence of CAR T cells varies depending on the CAR T construct but is often limited to a few months after second-generation CAR T cells[103]. However, the clinical benefits of anti-CD19 CAR T cell therapy persist beyond the presence of CAR T cells in the peripheral circulation; clinical benefits have been reported 3 years post-treatment. Despite its promise, careful longitudinal studies are needed to confirm these findings, optimize the treatment protocols and patient selection criteria, study the duration of the therapeutic effects and explore the molecular mechanisms underlying the effects on the different histopathological changes in SSc. Thus far, several clinical trials of autologous anti-CD19 CAR T cells in SSc from different companies are recruiting. In addition to autologous anti-CD19 CAR T cells, clinical trials of allogenic anti-CD19 CAR T cells are currently in preparation for SSc and other autoimmune diseases based on first reports of efficacy and safety in three patients with autoimmune rheumatic diseases, including two patients with dcSSc[107].

In addition to anti-CD19 CAR T cells, CAR T cells that target BCMA$^+$ B cells are currently being evaluated for the treatment of autoimmune diseases[108]. Although the initial results from case series are encouraging, further studies with additional patients and long-term follow-up are required. Moreover, high costs as well as complex organization might make widespread use outside of specialized centres challenging.

Case reports from the past year indicate the efficacy of bispecific T cell engagers (BiTEs) for the treatment of severe, refractory SSc[109,110]. These bispecific antibodies direct T cell-mediated cytotoxic activity against cells that express target antigens. BiTEs are fusion proteins consisting of two single-chain variable fragments of different antibodies. One of the single-chain variable fragments binds to and activates CD3 on T cells, and the other single-chain variable fragment binds to antigens on the target cell such as CD19. Binding of bispecific antibodies thus induces the formation of an immunological synapse between T cells and target cells, which causes T cells to exert cytotoxic activity on target cells by releasing perforin and granzymes, independently of the presence of other co-stimulatory molecules or MHC I[111]. One case report describes the successful treatment of a patient with severe, progressive SSc with blinatumomab (a CD19xCD3 BiTE)[109]. Three different case series demonstrate the efficacy of teclistamab (a BCMAxCD3 BiTE) in people with advanced, previously treatment-refractory SSc, although the total number of patients in these studies was less than ten[110] (and J.H.W.D., unpublished observations).

Anti-CD19 antibodies

Inebilizumab is a depleting, affinity-optimized, afucosylated humanized monoclonal anti-CD19 antibody that is approved for the treatment of neuromyelitis optica spectrum disorder in adult patients who are anti-aquaporin-4 antibody positive. Inebilizumab demonstrated good safety and tolerability in a phase I, randomized, placebo-controlled, escalating single-dose study in people with SSc[112]. Inebilizumab treatment at doses of 0.1–10.0 mg/kg led to dose-dependent depletion of circulating B cells and plasma cells in 24 people with SSc compared with 4 people who received placebo[112]. Interestingly, patients with a plasma-cell mRNA signature in biopsy-obtained skin samples at baseline showed greater improvement in mRSS following treatment with inebilizumab than patients with a low plasma-cell mRNA signature, which suggests that patient enrichment prior to therapy might be beneficial[113].

T cell-targeted approaches

In addition to the numerous approaches that target B cells, several therapies that alter T cell activation are being evaluated for the treatment of SSc.

OX40 ligand blockade

OX40 ligand (OX40L, also known as TNFSF4) is upregulated on activated antigen-presenting cells and interacts with OX40 on T cells, which promotes T cell proliferation, survival and context-dependent T_H1, T_H2 and T_H9 skewing and cytokine release. Moreover, OX40–OX40L signalling promotes germinal centre formation and humoral immunity by promoting T follicular helper cell development and supporting B cell responses[114]. In SSc, polymorphisms in *OX40L* are linked to disease susceptibility[115]. OX40L expression is increased in the fibrotic skin of patients with early, diffuse SSc at the protein and transcript levels[116,117]. Interestingly, OX40L is not only expressed in immune cells but also in dermal fibroblasts[116,117]. In a preclinical study, OX40L knockout or neutralizing OX40L antibodies abrogated fibrosis and the infiltration of macrophages and T cells, B cells and NK cells in the bleomycin-induced dermal fibrosis mouse model[116]. Similarly, neutralizing OX40L antibodies decreased pulmonary fibrosis in the Fra2 transgenic mouse model[116]. Amlitelimab is a fully human, non-depleting, non-cytotoxic anti-OX40 ligand monoclonal antibody that has shown promising efficacy and safety results for the treatment of atopic dermatitis in a phase IIa double-blind placebo-controlled study[118]. Amlitelimab will be examined for the treatment of SSc-ILD in the ongoing CONQUEST clinical trial platform[48] with the primary end point being FVC change from baseline after 52 weeks[48].

TL1A blockade

TNF-like cytokine 1A (TL1A – also known as TNFSF15) is a pro-inflammatory cytokine that belongs to the TNF superfamily. TL1A is expressed by immune cells during inflammation and exerts its functions via interactions with cell-surface death domain receptor 3 (DR3). Preclinical studies indicate that injection of TL1A into the airways of wild type mice induces a fibrotic response via interactions with DR3 in a T cell- and/or innate lymphoid cell-independent manner[119]. Moreover, genetic deletion of *DR3* attenuated increases in collagen deposition in the bleomycin-induced pulmonary fibrosis mouse model[119]. Serum TL1A levels were elevated in patients with SSc with late diffuse cutaneous involvement (disease duration >5 years) but not in those with early cutaneous involvement (disease duration <2 years) compared with matched healthy individuals[120]. Moreover, bulk RNA sequencing analysis revealed that *TL1A* gene expression was increased in SSc-ILD compared with healthy individuals[120]. Tulisokibart is a humanized monoclonal antibody that binds to the membrane-bound and soluble forms of TL1A, which prevents its interaction with DR3. In a phase II randomized, double-blind clinical trial, tulisokibart was effective at inducing clinical remission in patients with moderately to severely active ulcerative colitis and had an adequate safety profile[121]. Building on the aforementioned data, an ongoing phase II, randomized, placebo-controlled clinical trial is investigating the safety and efficacy of intravenous tulisokibart in SSc-ILD, with the primary outcome being FVC change from baseline after 50 weeks (NCT05270668).

Targeting IL-17 signalling

IL-17 comprises a family of cytokines, including IL-17A, IL-17B, IL-17C, IL-17D (also known as IL-27), IL-17E (also known as IL-25) and IL-17F. IL-17A and IL-17F form homodimers and/or heterodimers, both of

which interact with the same heterodimeric receptor, composed of the ubiquitously expressed IL-17 receptor A (IL-17RA) chain and the inducible IL-17 receptor C chain[122]. IL-17A is a pro-inflammatory cytokine mainly produced by T_H17 cells and has a key role in host defence against opportunistic pathogens such as *Candida albicans*[123]. This cytokine is also implicated in the pathogenesis of various inflammatory diseases, and might have a role in fibrotic tissue remodelling as suggested by experimental evidence from studies on fibrotic disease of the lungs, kidneys, heart and skin[124]. However, there are conflicting reports regarding the role of IL-17A in pathogenesis of SSc and its precise contribution to SSc pathogenesis remains unclear[125]. For instance, several studies report elevated circulating IL-17A levels in patients with SSc, whereas others have found no significant difference or even lower IL-17A levels[126–131]. $IL\text{-}17A^+$ cells are increased in the dermis of SSc skin, whereas $IL\text{-}17F^+$ cells do not increase. Functionally, IL-17A can stimulate the proliferation of SSc fibroblasts in vitro, but the direct stimulatory effects of this cytokine on collagen and extracellular matrix protein synthesis in fibroblasts seem to be minimal under standard cell-culture conditions[126,127,129]. Results from another study indicate that IL-17A might even inhibit collagen synthesis in vitro[127]. More pronounced effects of IL-17A on fibroblasts have been reported in 3D cultures[127]. In contrast to the limited effects on cultured fibroblasts, IL-17 blockade potently reduced fibrosis severity in various mouse models of skin fibrosis, including the bleomycin-induced fibrosis model, mice with chronic graft-versus-host disease and $TSK/^+$ mice[132]. The more pronounced effects of IL-17 blockade in mouse models might, in part, be explained by the effects of IL-17 on immune-cell recruitment, which is a critical pathophysiological feature in the bleomycin-induced fibrosis and chronic graft-versus-host disease mouse models.

Beyond fibrosis, IL-17A might also contribute to the vascular pathogenesis of SSc. IL-17A induces endothelial cells to release cytokines and chemokines, which promotes neutrophil infiltration via the ERK1–2 signalling pathway, but also triggers endothelial apoptosis, which exacerbates endothelial dysfunction[133]. Several biologic therapies that target IL-17A, IL-17F, both IL-17A and IL-17F, and IL-17RA are already approved for psoriasis, psoriatic arthritis, spondyloarthritis and inflammatory bowel disease. Notably, a phase III RCT with brodalumab, an IL-17RA antagonist that inhibits multiple IL-17 family members, in patients with SSc, was completed in Japan; however, the sponsor ultimately withdrew from publication of the results, leaving the potential of this therapeutic for SSc unresolved.

Targeting IL-23

IL-23 has a crucial role in the differentiation and maintenance of T_H17 cells, promoting the production of IL-17A and IL-22. IL-12 is composed of the IL-23-specific p19 subunit and the common p40 subunit, the latter of which is shared with IL-12. Monoclonal antibodies that target the p19 subunit, such as guselkumab and risankizumab, are approved for the treatment of psoriasis and psoriatic arthritis. Beyond its role in T_H17 cell expansion and IL-17A production, IL-23 also enhances B cell survival and autoantibody production. Although IL-23 is primarily regarded as pro-inflammatory, some studies suggest that it might also exhibit immune regulatory effects under certain conditions[134]. Further research is needed to clarify the precise role of IL-23 in SSc pathogenesis. Despite these uncertainties, a phase IIa, multicentre, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of guselkumab in patients with SSc has been completed (NCT04683029).

Other inflammation-modulating approaches

Combined inhibition of IL-17A and BAFF

Tibulizumab is a humanized tetravalent bispecific dual-antagonist antibody engineered to neutralize both BAFF and IL-17A[135]. By targeting these two pro-inflammatory cytokines, tibulizumab is aimed at modulating immune responses. As outlined previously, BAFF and IL-17A are both implicated in the pathogenesis of SSc. Potential synergistic effects between these two cytokines have been reported in a mouse model of bleomycin-induced lung fibrosis[114]. Specifically, the induction of BAFF expression was IL-17A dependent and BAFF in turn promoted IL-17A-driven fibrosis by stimulating IL-17A production by T cells. Tibulizumab is currently being investigated in a phase II, double-blind, placebo-controlled trial in early dcSSc (NCT06843239).

Type I interferon receptor blockade

There are several lines of evidence that indicate that interferon activation is involved in the pathogenesis of SSc. Several genes in the interferon pathways are associated with susceptibility to SSc[136]. Moreover, an interferon activation signature is the most prominent gene expression profile in peripheral blood cells from patients with SSc[137]. Prominent interferon signatures are found in affected end-organs such as the skin and lung[117,138]. Moreover, the levels of interferon-inducible chemokines in plasma are associated with SSc disease severity[139]. Last, evidence of the pathogenic role of type I interferon comes from an RCT of IFNα in patients with early diffuse SSc. In this trial, treatment with IFNα exacerbated rather than improved skin and lung fibrosis[140], although it was initially hypothesized that this treatment would improve fibrosis owing to observed inhibitory effects of IFNα on collagen synthesis in fibroblasts in vitro[141]. Anifrolumab is a fully human, monoclonal antibody that targets the type I interferon receptor α subunit 1 (IFNAR1). As all interferon α and β subtypes signal via IFNAR, this therapy can effectively block downstream type I interferon signalling. Anifrolumab is approved for the treatment of moderate-to-severe SLE; interferon signatures similar to those in SSc are observed in SLE. Anifrolumab demonstrated adequate safety and tolerability in a phase I trial in patients with SSc[134,142]. In this trial, anifrolumab suppressed the type I interferon gene expression signature in whole blood and skin, demonstrating adequate target engagement. Analysis of serial skin samples collected prior to treatment initiation and 28 days post-treatment revealed that blocking IFNAR1 blockade was also associated with suppression of extracellular matrix-related transcripts, including type I collagen[143,144]. A multinational, randomized, placebo-controlled, double-blind phase III clinical trial has been launched to determine the efficacy of subcutaneous anifrolumab in SSc. This trial permits background immunosuppression and the primary efficacy end point is a revised CRISS-25 response at 52 weeks (NCT05925803).

Neuropilin-2 modulation

Histidyl-tRNA synthetase (HARS) is one of several aminoacyl tRNA synthetase enzymes that catalyse the esterification of tRNA to its corresponding amino acid based on its base sequence. These enzymes are essential for the translation of mRNAs to an accurate amino acid sequence. Specifically, HARS is responsible for the incorporation of histidine into a growing peptide. Although this process occurs intracellularly, fragments and splice variants of tRNA synthetase are also present extracellularly[145]. The gene encoding HARS gives rise to several splice variants. One HARS splice variant, which only contains the N-terminal domain (HARS amino acids 1–60), is enriched in human lung tissue, and its expression is increased following stimulation with

pro-inflammatory cytokines, such as interferon and TNF[146]. Notably, the N-terminal domain of HARS is targeted by the anti-Jo-1 antibody, which is the most common antibody associated with anti-synthetase syndrome, a systemic autoimmune disease that frequently leads to ILD[147]. Detectable circulating free HARS can be identified in sera from healthy people but not in sera from patients with anti-Jo-1 antibody-positive anti-synthetase syndrome[148]. Moreover, recombinant HARS decreases T cell activation and cytokine release[148]. Cumulatively, these data support the hypothesis that sequestration of HARS through anti-Jo-1 antibodies leads to disruption of immune homeostasis. HARS has a short half-life, but the therapeutic drug efzofitimod contains a HARS amino acid sequence (amino acid 2–60) that is fused with the Fc portion of human IGg1, which extends its half-life. In a follow-up experiment, Neuropilin-2 (NRP2) was identified as the sole binding partner for efzofitimod[146,149]. NRP2 is a cell-surface receptor that is expressed on several immune cells, such as macrophages, and has a role in myeloid-cell biology, including cell differentiation. NRP2 is highly expressed on macrophage populations within the granulomas of patients with sarcoidosis[150]. Efzofitimod decreased immune-cell counts in the lung tissue and bronchoalveolar lavage in a lipopolysaccharide acute lung inflammation mouse model[146]. Building on these preclinical findings, the safety and efficacy of efzofitimod were investigated in a randomized, double-blind, placebo-controlled phase II–III clinical trial in patients with pulmonary sarcoidosis[151]. Efzofitimod was generally well tolerated and showed non-significant trends towards improved FVC and glucocorticoid reduction. Building on the aforementioned results, a double-blind, randomized, placebo-controlled phase II study has been launched to evaluate the safety and efficacy of efzofitimod in SSc-ILD. The primary outcome of this ongoing trial is the absolute change from baseline in FVC (NCT05892614).

Anti-fibrotic approaches with vascular effects

Vascular manifestations of SSc are a leading cause of morbidity and contribute to overall mortality. Moreover, vascular manifestations might promote fibroblast activation and tissue fibrosis directly via endothelial-to-mesenchymal transition[152,153], release of profibrotic mediators from endothelial cells[154], platelet activation at the damaged endothelium[155] or indirectly by vasculopathy-induced hypoxia[154]. Therapeutics that interfere with vascular and fibrotic features of SSc might thus exert additive effects on fibrotic tissue remodelling and simultaneously address two key medical needs in SSc.

Activators of soluble guanylate cyclase

Soluble guanylate cyclase (sGC) is an enzyme that catalyses the conversion of GTP to cyclic guanosine monophosphate (cGMP), when nitric oxide is bound to a prosthetic haem group on sGC[156,157]. cGMP is an anti-fibrotic mediator that limits TGFβ-induced ERK phosphorylation and fibroblast activation[157]. Preliminary evidence indicates that cGMP might also reduce the release of profibrotic mediators from cultured endothelial cells and limit type I interferon signalling in bleomycin-induced fibrosis in mice[158]. cGMP transmits its anti-fibrotic effects in part via protein kinase G (PKG1 and PKG2); however, chronic exposure of fibroblasts to TGFβ downregulates the expression of PKGs[159], thereby partially desensitizing fibroblasts to the anti-fibrotic effects of cGMP. Another mechanism that might contribute to inhibition of sGC–cGMP signalling in SSc is oxidative stress, which leads to the formation of an oxidized, haem-free form of sGC that is unresponsive to nitric oxide. Two different types of drugs have been developed to activate sGC signalling. sGC stimulators require haem-bound sGC and enhance sGC sensitivity to nitric oxide, whereas sGC activators bind directly to haem-free sGC and can activate the enzyme independently of nitric oxide. sGC stimulators and sGC activators both show anti-fibrotic effects in vitro and in mouse models of SSc[156,158,160].

In a phase II RCT of the sGC stimulator riociguat in patients with dcSSc, treatment showed a beneficial trend for mRSS as the primary outcome, and for several secondary readouts including FVC, but did not reach statistical significance[161]. Based on these findings and the hypothesis that sGC activators might be more effective in upregulating cGMP levels than sGC stimulators in a disease with high levels of oxidative stress and accumulation of oxidized, haem-free sGC, a placebo-controlled, double-blind, parallel-group phase II clinical trial of the sGC activator avenciguat in patients with SSc-ILD is currently recruiting, with the primary outcome being changes in FVC after 48 weeks (NCT05559580).

Targeting the thromboxane prostanoid receptors

The thromboxane prostanoid receptor (TPR, encoded by *TBXA2R*) is activated by thromboxane and prostanoids and induces constriction of vascular smooth muscle cells, promotes platelet aggregation and induces pro-inflammatory responses in endothelial cells. Moreover, aberrant TPR signalling might be implicated in the pathogenesis of fibrotic remodelling of the lungs and heart and of pulmonary arterial hypertension[162–164].

Lung fibroblasts upregulate TPR expression during fibrosis, with increased expression levels in patients with IPF and in mice with experimental fibrosis[162]. Genetic deletion of *Tbxa2r* protected mice from bleomycin-induced lung fibrosis, suggesting the functional role of TPR signalling in fibrotic tissue remodelling[162]. TPR activation does not predominantly occur via thromboxanes in this model, as inhibition of thromboxane synthase did not ameliorate fibrosis. F2-isoprostanes, which are non-enzymatic products of arachidonic acid induced by reactive oxygen species, might account for the activation of TPR. F2-isoprostanes are elevated during experimental fibrosis and can activate TPR signalling in fibroblasts and induce fibroblast-to-myofibroblast transition in vitro. Pharmaceutical inhibition by the selective, orally bioavailable TPR antagonist ifetroban ameliorated bleomycin-induced fibrosis and radiation-induced experimental fibrosis and reduced fibrotic remodelling in a mouse model of Hermansky–Pudlak syndrome[162].

Preclinical studies also provide evidence of the use of TPR antagonists to treat PAH and associated right heart failure. In a rat model of monocrotaline-induced PAH, treatment with the TPR antagonist NTP42 also alleviated pulmonary vascular remodelling, inflammation and fibrosis in monocrotaline-challenged rats[163]. These histological changes were associated with improved clinical readouts of PAH with reduction in mean pulmonary arterial pressure and right systolic ventricular pressure in rats treated with NTP42 (ref. 163). These beneficial effects of the TPR antagonist might be mediated by a combination of anti-fibrotic, anti-inflammatory, anti-proliferative and vasodilative effects in combination with inhibitory effects on platelet aggregation. TBXA2R inhibition also ameliorated fibrotic remodelling of the right ventricle and TGFβ signalling in a mouse model of right heart failure induced by pulmonary artery banding[164], a common model of PAH-induced right heart failure.

The safety and efficacy of the TPR antagonist ifetroban is currently being investigated in a randomized, double-blind and placebo-controlled phase II clinical study in people with diffuse dcSSc or SSc-associated pulmonary arterial hypertension (NCT02682511).

The future of drug development in systemic sclerosis

Despite progress with the approval of novel medications and major increases in the number of clinical trials in SSc compared with previous decades, several potential targets for therapeutic intervention with promising preclinical data have not yet been translated from bench to bedside.

Targeting epigenetic modifications in SSc might have therapeutic potential but this approach has not yet been used in clinical practice. Various epigenetic modifications, such as DNA methylation, and different histone methylation and acetylation markers are altered in SSc[70,165–177]. These epigenetic changes are thought to maintain an SSc-specific, activated cellular phenotype particularly in less inflammatory stages of disease and might thus promote disease progression in later stages of SSc. Targeted modification of these epigenetic alterations with genetic and pharmacological approaches in cultured cells from patients with SSc and in mouse models of fibrosis show therapeutic effects in preclinical assays with amelioration of the SSc-specific cellular phenotype and reduced fibrotic remodelling[70,175,177–179]. Although several epigenetic drugs such as DNA-methyltransferase inhibitors or histone-deacetylase inhibitors are in clinical use in oncology, these findings have not been investigated in interventional clinical trials in SSc.

Aberrant cellular senescence is also emerging as a central pathomechanism in SSc and in other fibrotic diseases[180,181]. Accumulating evidence demonstrates that immunosenescence might promote disease progression by directly altering cell functions or indirectly by defective immune surveillance[180,181]. First proof-of-concept studies with senotherapeutics showed encouraging results in other fibrotic diseases; however, these compounds are currently not specific to senescence and can have broader effects[180].

Another emerging area is targeting individual cell subpopulations that are relevant to disease pathogenesis rather than broad, unselective targeting of entire cell types. Advances in single-cell omics technologies have facilitated the identification of phenotypically and functionally distinct subpopulations of cells in health and disease. These studies demonstrate shifts in the proportion of individual subpopulations rather than general changes in cell phenotype in chronic diseases such as SSc. For example, even in affected skin from patients with highly active, progressive SSc, not all fibroblasts display an activated, profibrotic phenotype, but profibrotic and pro-inflammatory fibroblast subpopulations such as CCL19$^+$ fibroblasts, SFRP4$^+$SFRP2$^+$ fibroblasts, ADAM12$^+$GLI1$^+$ fibroblasts or S1PR$^+$ fibroblasts expand, whereas the number of homeostatic cell subpopulations such as PI16$^+$ fibroblasts and TFAM^{high} fibroblasts decrease[182,183]. Selectively targeting these disease-promoting subpopulations of cells rather than broader cell populations might minimize treatment-related adverse events; however, specifically targeting these defined cell subpopulations can be challenging, as most are defined by combinations of several different markers rather than by specific individual markers. However, surrogate markers can be defined for many of these subpopulations, which enables preferential, but not entirely specific, targeting of disease-relevant cell subpopulations.

Another emerging area for the treatment of SSc is precision medicine. Although precision medicine with a specific treatment regimen for individual patients is common in oncology, precision medicine approaches to rheumatic diseases are scarce. However, precision-medicine approaches with upfront selection of effective therapies would be particularly important in fibrotic diseases, in which responses to therapies can be assessed only after prolonged follow-up of often 6 or even 12 months, thus leading to potentially long periods on suboptimal or even insufficient therapies. Emerging approaches to precision medicine in SSc include upfront evaluation of molecular responses to treatments in ex vivo cultures of precision-cut slices of skin from patients with subsequent omics-based profiling of molecular responses to individual treatments. Initial results indicate that molecular responses might be predictive of clinical responses to the respective drugs; thus, drug selection for individual patients could potentially be based on molecular responses in skin samples from people with SSc (J.H.W.D., unpublished observations). However, these approaches require confirmation in larger cohorts with longer follow-up. Such an approach would require upfront biopsies, generation of precision-cut slices, standardized exposure to test drugs and standardized evaluation of molecular responses, which would need to be established across different centres before broader use.

Conclusions

SSc has become a major focus of active and expanding drug development, with successful approval of novel targeted therapies over the past 5 years and promising ongoing clinical trials targeting different molecular and cellular entities. These clinical trials might yield additional therapeutic approaches to further reduce the high morbidity and mortality associated with SSc. With the approval of additional treatments, personalized medicine strategies for the selection of optimal treatments for each patient need to be developed to avoid prolonged periods of suboptimal or even ineffective treatment.

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

J.H.W.D. has consultancy relationships with Active Biotech, Anamar, ARXX, AstraZeneca, Bayer Pharma, Boehringer Ingelheim, Callidatas, Calluna, Galapagos, GSK, Johnson&Johnson, Kyverna, MSD, Novartis, Prolium, Quell Therapeutics and UCB, has research funding from Anamar, ARXX, BMS, Boehringer Ingelheim, Cantargia, Celgene, CSL Behring, Exo Therapeutics, Galapagos, GSK, Incyte, Inventiva, Kiniksa, Kyverna, Lassen Therapeutics, Mestag, Sanofi-Aventis, SpicaTx, RedX, UCB and ZenasBio, and is CEO of 4D Science and scientific lead of FibroCure. M.K. has received consultancy fees, speaking fees, and research grants from AbbVie, Argenx, Asahi Kasei, AstraZeneca, Boehringer Ingelheim, Chugai, GlaxoSmithKline, Janssen, Kissei, MBL, Mitsubishi Tanabe, Mochida, Novartis and Ono Pharmaceuticals. S.A. reports grants paid to his institution from Boehringer Ingelheim, the Scleroderma Research Foundation, Janssen and aTyr, as well as consultancy fees from AbbVie, AstraZeneca, aTyr, Boehringer Ingelheim, CSL Behring, Merck, Mitsubishi Tanabe, Takeda, and TeneoFour. C.P.D. has consultancy relationships with GlaxoSmithKline, Johnson&Johnson, Bayer, Sanofi, Boehringer Ingelheim, Roche, CSL Behring, Corbus, Acceleron, Horizon, Arxx, Lilly, Novartis, Certa, Mitsubishi, Quell and research grant funding from AbbVie, Arxx, Horizon, GlaxoSmithKline, CSL Behring and Servier.

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