World's largest Science,
Technology & Medicine
Open Access book publisher

3,250+
OPEN ACCESS BOOKS

106,000+
INTERNATIONAL
AUTHORS AND EDITORS

112+ MILLION
DOWNLOADS

BOOKS
DELIVERED TO
151 COUNTRIES

AUTHORS AMONG
TOP 1%
MOST CITED SCIENTIST

12.2%
AUTHORS AND EDITORS
FROM TOP 500 UNIVERSITIES

CLARIVATE ANALYTICS
**BOOK
CITATION
INDEX**
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the
Book Citation Index in Web of Science™
Core Collection (BKCI)

Interested in publishing with InTechOpen?
Contact us at book.department@intechopen.com

Translating Autoimmune Pathogenesis into Targeted Therapies for Systemic Sclerosis

Mark D. Russell and Nidhi Sofat

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/66642

Abstract

Targeted therapies including tumour necrosis factor α (TNFα) inhibitors have transformed the management of a number of autoimmune conditions over the past 20 years. One autoimmune rheumatological condition with significant potential for the development of targeted therapies is systemic sclerosis (SSc). In this chapter, we use SSc as an example of how research into the pathogenic processes underlying autoimmune conditions can be translated into novel targeted therapies. We review the evidence base for a range of targeted therapies for SSc identified from a systematic literature search, before highlighting a number of studies currently underway.

Keywords: systemic sclerosis, scleroderma, targeted therapies, biological therapy, biologic, rheumatology, rheumatoid arthritis, autoimmune

1. Introduction

1.1. Targeted therapies in autoimmune conditions

Targeted therapies have revolutionised the management of many autoimmune rheumatological conditions over the last 20 years. Ground-breaking research in the early 1990s identified tumour necrosis factor alpha (TNFα) as a key inflammatory mediator of rheumatoid arthritis [1–6]. This research enabled the development of targeted TNFα inhibitors, such as adalimumab, infliximab and etanercept. Although costly, these therapies have greatly improved the outlook for patients with severe, active rheumatoid arthritis [7, 8].

As we improve our understanding of the pathogenic processes underlying rheumatoid arthritis, the number of potential targets for novel therapies increases. Several additional tar-

geted therapies are now licensed for the treatment of patients with severe rheumatoid arthritis who have failed to respond adequately to, or been unable to tolerate, conventional immunosuppressive therapies. Examples include: rituximab, a B-lymphocyte-depleting monoclonal antibody targeting the CD20 antigen; abatacept, a fusion protein that abrogates the co-stimulatory signals required for the activation of T-lymphocytes; tocilizumab, an interleukin (IL)-6 receptor antagonist; and anakinra, an IL-1 receptor antagonist [8–13].

The process of translating research on autoimmune pathogenesis into targeted therapies has not been limited to rheumatoid arthritis, however. TNFα inhibitors have also been shown to be highly effective in psoriasis and psoriatic arthritis, as well as ankylosing spondylitis, juvenile idiopathic arthritis and inflammatory bowel disease [14–17]. Targeted therapies with novel mechanisms of action have also been developed for a number of autoimmune rheumatological conditions. Ustekinumab, a humanised monoclonal antibody directed against IL-12/23, is licensed as a treatment for both psoriasis and psoriatic arthritis [18]. Secukinumab, an IL-17 inhibitor, has also been shown to be efficacious in the treatment of both psoriasis and psoriatic arthritis [19, 20]. In the case of autoantibody-positive systemic lupus erythematosus, belimumab, an inhibitor of B-lymphocyte stimulator, has recently been licensed as an adjunctive therapy [21].

An autoimmune rheumatological condition with a great need for targeted therapies is systemic sclerosis (SSc). In this chapter, we use SSc as an example of how research into pathogenic processes can be translated into novel therapeutic targets for autoimmune conditions.

1.2. Background to systemic sclerosis

SSc is a multi-system autoimmune condition that typically arises between the ages of 30 and 50 years, with women affected approximately four times more frequently than men. The aetiology of SSc remains to be elucidated and is likely to involve complex interactions between environmental factors in genetically predisposed individuals. Multiple cell types, cytokines and signalling pathways contribute to three sustained and interdependent pathogenic processes that form the hallmark of SSc: excessive extracellular matrix production and deposition by fibroblasts, inflammation and vascular abnormalities [22]. These processes culminate in multi-organ fibrosis, in addition to vascular manifestations, such as pulmonary arterial hypertension (PAH), Raynaud's phenomenon (RP) and renal crises.

Fibrotic thickening and hardening of the skin, termed sclerodactyly, can lead to profound physical and psychological morbidity. Gastrointestinal tract fibrosis can produce a range of complications depending on the portions of the tract involved, including oesophageal reflux and strictures, gastroparesis, small bowel bacterial overgrowth and constipation. Pulmonary involvement represents the leading cause of death in patients with SSc, with interstitial lung disease (ILD) and PAH typically presenting with progressive breathlessness on exertion. Two additional presenting features of SSc, often occurring in the early stages of the disease, are digital swelling and RP. In the case of the latter, vasospastic changes produce a characteristic whitening of the distal portions of the fingers and toes that progresses to a blue discolouration (representing cyanosis), before flushing red as blood flow returns. In SSc, RP can be severe enough to result in digital ulceration and necrosis.

SSc can be subdivided into two main forms depending on the extent of skin involvement. In limited cutaneous systemic sclerosis (lcSSc), fibrosis occurs in the skin of the face and in the skin distal to the elbows and knees. A term often used interchangeably with lcSSc is CREST syndrome, an acronym representing five cardinal signs and symptoms that arise in a subset of patients with lcSSc: calcinosis, RP, oesophageal dysmotility, sclerodactyly and telangiectasia. Diffuse cutaneous systemic sclerosis (dcSSc) is characterised by more extensive skin involvement than lcSSc, such that the proximal arms, legs and trunk are often affected. The onset and progression of skin changes are usually more rapid in dcSSc than in lcSSc, with multi-organ fibrosis typically occurring to a greater extent.

1.3. Management of systemic sclerosis

The mainstay of management of SSc involves close monitoring for systemic complications, with treatment as they arise [22]. A multidisciplinary approach is essential, with involvement of clinicians from a range of specialties, as well as physiotherapists, occupational therapists and psychologists [23, 24].

For skin involvement, topical steroids and emollients can help to ameliorate any associated pruritus and xerosis. Camouflage products are also effective in minimising the cosmetic effects of hypopigmented and hyperpigmented areas of skin, as well as telangiectasia. Regular physiotherapy, along with orthoses, decreases the risk of sclerodactyly-induced contractures. However, surgery may ultimately be required in the case of established contractures.

Acid-suppressant therapies, such as proton-pump inhibitors, and pro-motility agents, such as metoclopramide, are frequently used to treat SSc-associated gastro-oesophageal reflux and gastroparesis, respectively. Should strictures of the oesophagus arise, endoscopic dilatation can be employed. With more distal gastrointestinal tract involvement, dietetic input can help to counter the malabsorptive effects of small bowel dysmotility and bacterial overgrowth. The latter may also necessitate cyclical treatment with antibiotics. Laxative therapy, pro-motility agents and ensuring an adequate intake of fibre can minimise the constipation that arises from colonic dysmotility.

A potentially fatal complication of SSc, requiring emergent treatment, is a scleroderma renal crisis. This typically presents with acute-onset hypertension and renal impairment, and can rapidly progress to renal failure without prompt recognition and treatment. Angiotensin-converting enzyme inhibitors are the cornerstone of management of such crises. Their use has greatly improved the prognosis associated with scleroderma renal crises, such that this complication is no longer the leading cause of death in patients with systemic sclerosis.

Significant progress has also been made in the management of SSc-associated RP. Treatment options available include calcium-channel blockers, such as nifedipine, phosphodiesterase type-5 inhibitors, such as sildenafil, and angiotensin II receptor antagonists, such as losartan. In cases of digital ulceration and impending digital necrosis, inpatient admission may be required for intravenous prostanoid therapy. Phosphodiesterase type-5 inhibitors and prostaglandin infusions are also effective treatments for SSc-associated PAH. Additionally, bosentan, an endothelin-receptor antagonist, has been shown to be efficacious in the manage-

ment of both SSc-associated PAH and digital ulcers. Bosentan is a rare example of a targeted therapy licensed for use in SSc and is covered in greater detail later in this chapter.

Multiple immunosuppressive medications have been trialled in SSc. The evidence base is weak, however, and clinical trials of such medications are limited by the rarity and heterogeneity of SSc, and the variability in the natural progression of the disease. As is true of other autoimmune rheumatological conditions, there is a growing trend for early, aggressive treatment of SSc with immunosuppressive regimens [23, 24]. This is particularly true of dcSSc, where early immunosuppression has the potential to stem the progression of the disease. Typical first-line treatment options for SSc-associated ILD include intravenous cyclophosphamide (as induction therapy) followed by an oral agent such as mycophenolate mofetil (as maintenance therapy). In cases of extensive SSc-associated skin fibrosis, treatment options include mycophenolate mofetil and methotrexate, as well as azathioprine, cyclophosphamide and corticosteroid therapy [24].

Relative to other autoimmune conditions, such as rheumatoid arthritis, the efficacy of immunosuppressive regimens in the treatment of SSc is modest [25]. Broad-spectrum immunosuppression also carries with it the risk of infection and bone marrow suppression, as well as agent-specific side effects, such as bladder toxicity with cyclophosphamide therapy. As such, there is a concerted effort to find novel treatment options for SSc. One example is autologous haematopoietic stem cell transplantation, which has a growing evidence base in SSc. In selected patients with early dcSSc and poor prognostic features, stem cell transplantation has been shown to improve long-term event-free and overall survival rates, relative to IV cyclophosphamide [26, 27]. These benefits have to be weighed against early transplant-related mortality rates of 10%, however. As such, the use of stem cell transplantation is restricted to those patients with early dcSSc who are yet to develop severe organ involvement. Another example of an emerging therapy is intravenous immunoglobulin (IVIg), with a number of pilot studies reporting improvements in skin fibrosis scores, gastrointestinal manifestations and joint-related symptoms [28–31].

Despite some progress in the management of SSc, there remains a great need for therapies that target the specific pathogenic processes underlying the disease, namely fibrosis, inflammation and vascular damage. The development of efficacious targeted therapies has the potential to transform the management of this disabling condition, just as TNFα inhibitors have done in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. In this chapter, we use SSc as an example of how research into pathogenic processes can be translated into novel therapeutic targets for autoimmune conditions.

2. Body

We performed a systematic search of the PubMed and Cochrane medical literature databases to identify all clinical studies involving therapeutic interventions in patients with systemic sclerosis during the last 10 years (covering the period of July 2006–June 2016). Using a broad search strategy, we identified 2381 articles. We reviewed the abstracts of these articles and

selected those studies involving therapies with targeted mechanisms of action, that is, treatments targeting specific molecular and/or cellular pathways known to be involved in the pathogenesis of SSc. Studies were excluded if they were not written in English, if they did not involve human subjects or if they had less than three study subjects. In total, 69 studies were identified and the details are shown in **Table 1**. The majority of the therapies identified can be grouped into three broad categories, corresponding to which of the central pathogenic processes they target: fibrosis, inflammation or vascular abnormalities. It is important to note, however, that these processes are very much interdependent and, as such, targeting one pathway is likely to impact on one or more of the other processes [32].

Study treatment	Ref.	Treatment dosage	Disease aspect studied	Study type	Duration of study	Number drug/ control	*p*-value (measure)
Fibrosis							
TGF-β pathway inhibitors							
CAT-192	[35]	Various	dcSSc	RCT	6 months	32/11	>0.05 (mRSS)
Fresolimumab	[37]	Various	dcSSc	Prospective	24 weeks	15/0	<0.001 (mRSS)
Pirfenidone	[42]	2403 mg daily	SSc-ILD	Prospective	16 weeks	63/0	>0.05 (PFTs, mRSS)
Pirfenidone	[43]	1200/1800 mg daily	SSc-ILD	Case series	Various	5/0	N/A
Tyrosine kinase inhibitors							
Imatinib mesylate	[45]	400 mg daily	dcSSc	RCT	6 months	9/1	>0.05 (mRSS)
Imatinib mesylate	[46]	600 mg daily	SSc-ILD	Prospective	12 months	20/0	>0.05 (PFTs), <0.001 (mRSS)
Imatinib mesylate	[47]	400 mg daily	dcSSc	Prospective	12 months	30/0	<0.001 (mRSS), 0.008 (FVC)
Imatinib mesylate	[48]	400 mg daily	dcSSc	Prospective	36 months	17/0	0.002 (mRSS)
Imatinib mesylate	[49]	200 mg daily	SSc-ILD	Prospective	12 months	30/0	N/A
Imatinib mesylate	[126]	400 mg daily	SSc/ morphoea	RCT	12 months	15/13	>0.05 (mRSS)
Imatinib mesylate	[127]	200 mg daily	SSc	Case series	23 months	6/0	N/A
Imatinib mesylate	[128]	100 mg daily	SSc skin	Case series	6 months	3/0	N/A
Imatinib mesylate + CYC	[129]	200 mg daily	SSc-ILD	Case series	12 months	5/0	N/A
Nilotinib	[50]	800 mg daily	dcSSc	Prospective	12 months	10/0	0.02 (mRSS)
Other agents							

Study treatment	Ref.	Treatment dosage	Disease aspect studied	Study type	Duration of study	Number drug/ control	p-value (measure)
Oral type I collagen	[51]	500 µg daily	dcSSc	RCT	15 months	83/85	>0.05 (mRSS)
Relaxin	[53]	10/25 µg/kg daily	dcSSc	RCT	24 weeks	137/94	>0.05 (mRSS)
Inflammation							
TNFα inhibitors							
TNFα inhibitors	[54]	Various	SSc	Retrospective	Various	65/0	N/A
Etanercept	[60]	50 mg/week	SSc-m'skel	Retrospective	Various	18/0	>0.05 (HAQ, mRSS)
Infliximab	[61]	5 mg/kg ×5	dcSSc	Prospective	26 weeks	16/0	>0.05 (mRSS, HAQ)
Selective co-stimulation modulators							
Abatacept	[67]	500/1000 mg ×7	dcSSc	RCT	24 weeks	7/3	0.06 (mRSS)
Abatacept + tocilizumab	[68]	Various	SSc-m'skel	Observational	11 months	27/0	<0.001 (DAS28)
Abatacept	[130]	500/750 mg/4 weeks	dcSSc	Case series	Various	4/0	N/A
IL-2α inhibitors							
Basiliximab	[72]	20 mg ×6	dcSSc	Prospective	68 weeks	10/0	0.015 (mRSS), >0.05 (FVC/DLco)
IL-6 inhibitors							
Tocilizumab + abatacept	[68]	Various	SSc-m'skel	Observational	5 months	27/0	0.001 (DAS28)
Tocilizumab	[77]	8 mg/kg/4 weeks	SSc	Case series	Various	3/0	N/A
Tocilizumab	[78]	162 mg/week	SSc	RCT	48 weeks	43/44	0.09 (mRSS)
B-cell depletion							
Rituximab	[81]	Various	SSc	Case-control	Various	63/25	0.03 (mRSS), 0.02 (FVC)
Rituximab	[82]	1000 mg ×2	dcSSc	Prospective	6 months	15/0	>0.05 (mRSS)
Rituximab	[83]	(500 mg ×2)/3 months	SSc-ILD	Case series	12 months	5/0	<0.001 (mRSS, DLco), <0.004 (FVC)
Rituximab	[84]	1000 mg ×2	dcSSc	Prospective	24 weeks	8/0	<0.001 (mRSS)
Rituximab	[85]	1000 mg ×2	SSc	Prospective	36 months	9/0	0.001 (mRSS)

Study treatment	Ref.	Treatment dosage	Disease aspect studied	Study type	Duration of study	Number drug/ control	*p*-value (measure)
Rituximab	[86]	(375 mg/m² ×4)/6 months	dcSSc	Prospective	12 months	25/0	0.001 (FVC), 0.008 (DLco), 0.0001 (mRSS)
Rituximab	[87]	(375 mg/m² ×4)/24 weeks	SSc	RCT	12 months	8/6	0.002 (FVC), <0.001 (mRSS)
Rituximab	[88]	(375 mg/m² ×4)/6 months	SSc-ILD	Prospective	24 months	8/0	<0.0001 (FVC, mRSS), <0.001 (DLco)
Rituximab	[89]	(1000 mg ×2)/6 months	dcSSc	Prospective	24 months	8/0	<0.0001 (mRSS, DAS)
Rituximab	[90]	Various	SSc	Prospective	7 years	30/0	0.018 (FVC), 0.012 (DLco), <0.001 (mRSS)
MEDI-551	[91]	Various	SSc	RCT	85 days	24/4	N/A
Type I IFN receptor antagonists							
MEDI-546	[92]	Various	SSc	Prospective	12 weeks	34/0	N/A
Vascular							
Endothelin receptor antagonists							
Bosentan	[97]	250 mg daily	SSc-RP/skin	Retrospective	48 weeks	14/0	<0.05 (RP attacks), <0.01 (mRSS)
Bosentan	[99]	250 mg daily	SSc-PAH	Prospective	Various	49/0	0.014 (NYHA class), >0.05 (6MWD)
Bosentan	[100]	250 mg daily	SSc-DU	RCT	24 weeks	98/90	0.04 (DU episodes), >0.05 (DU healing)
Bosentan	[101]	250 mg daily	SSc-DU	Retrospective	24 months	67/0	N/A
Bosentan	[102]	250 mg daily	SSc-DU	Prospective	36 months	26/0	<0.001 (DU number)
Bosentan	[103]	62.5–125 mg daily	SSc-DU	Case series	Various	6/0	N/A
Bosentan	[108]	250 mg daily	SSc-RP	Prospective	16 weeks	15/0	<0.05 (RP attacks)
Bosentan	[112]	250 mg daily	SSc-ILD	RCT	12 months	77/86	>0.05 (6MWD, PFTs)
Bosentan	[113]	250 mg daily	SSc-ILD	Prospective	24 months	9/0	N/A

Study treatment	Ref.	Treatment dosage	Disease aspect studied	Study type	Duration of study	Number drug/ control	p-value (measure)
Bosentan	[114]	250 mg daily	SSc-skin	Prospective	24 weeks	10/0	<0.001 (mRSS, DU healing)
Bosentan + iloprost	[131]	250 mg daily	SSc-vascular	Observational	3 years	13/13	<0.01 (PBP)
Bosentan	[132]	250 mg daily	SSc-DU/PAH	Prospective	Various	54/0	<0.001 (DU episodes)
Bosentan	[133]	250 mg daily	SSc-NDU	Case series	Various	5/0	N/A
Bosentan	[134]	250 mg daily	SSc-vascular	Prospective	16 weeks	30/30	N/A
Bosentan	[135]	250 mg daily	SSc-RP	RCT	24 weeks	9/8	>0.05 (RP attacks), 0.01 (HAQ)
Bosentan	[136]	250 mg daily	CTD-PAH/ skin	Observational	24 months	15/0	<0.01 (6MWD, mRSS),
Bosentan	[137]	250 mg daily	CTD-PAH	Prospective	48 weeks	53/0	N/A
Bosentan	[138]	250 mg daily	SSc-DU	Prospective	Various	15/0	<0.05 (DU number)
Bosentan	[139]	125 mg daily	SSc-vascular	Prospective	4 weeks	12/12	<0.001 (FMD)
Bosentan	[140]	250 mg daily	SSc-vascular	Prospective	6 months	18/0	>0.05 (multiple measures)
Bosentan	[141]	250 mg daily	SSc-RP	Observational	16 weeks	3/0	N/A
Bosentan	[142]	250 mg daily	SSc-PAH	Prospective	6 months	8/0	0.01 (6MWD)
Bosentan	[143]	250 mg daily	SSc-DU	Prospective	12 weeks	52/51	<0.05 (blood flow)
Bosentan	[144]	250–500 mg daily	CTD-PAH	RCT	12-16 weeks	44/22	>0.05 (6MWD)
Ambrisentan + tadalafil	[105]	10 + 40 mg	SSc-PAH	Prospective	36 weeks	24/0	<0.05 (RV mass), <0.0001 (PVR)
Ambrisentan	[106]	5–10 mg daily	SSc-PAH	Prospective	24 weeks	12/0	0.004 (PVR), 0.003 (6MWD)
Ambrisentan	[107]	5 mg daily	SSc-DU/RP	Prospective	6 months	6/0	<0.03 (DU healing), 0.01 (RP attacks)
Ambrisentan	[145]	Up to 10 mg/day	SSc-DU	Prospective	24 weeks	20/0	0.004 (DU number)/0.0001 (DU diameter)
Ambrisentan	[146]	10 mg daily	SSc-vascular	RCT	12 weeks	15/5	>0.05 (blood flow), 0.005 (HAQ)

Study treatment	Ref.	Treatment dosage	Disease aspect studied	Study type	Duration of study	Number drug/ control	*p*-value (measure)
Macitentan	[115]	3/10 mg daily	SSc-DU	RCT (x2)	16 weeks	192/97 176/89	>0.05 (DU formation)
Other agents							
Fasudil	[116]	40/80 mg	SSc-RP	RCT crossover	Various	17/0	>0.05 (blood flow recovery)
ORM-12741	[117]	30/100 mg	SSc-RP	RCT crossover	Various	12/0	>0.05 (blood flow recovery)

Ref. = study reference, *Number drug/control* = number of subjects in the treatment and control arms of the study, and *p-value (measure)* = statistical significance of the outcome measure defined in brackets.

TNFα, tumour necrosis factor alpha; *CYC,* cyclophosphamide; *SSc,* systemic sclerosis; *dcSSc,* diffuse cutaneous systemic sclerosis; *CTD,* connective tissue disorder; *SSc-ILD,* systemic sclerosis-associated interstitial lung disease; *SSc-m'skel,* systemic sclerosis-associated musculoskeletal manifestations; *SSc-skin,* systemic sclerosis-associated skin manifestations; *SSc-vascular,* systemic sclerosis-associated vascular manifestations; *SSc-DU,* systemic sclerosis-associated digital ulcers; *SSc-PAH,* systemic sclerosis-associated pulmonary arterial hypertension; *SSc-NDU,* systemic sclerosis-associated nondigital ulceration; *SSc-RP,* systemic sclerosis-associated Raynaud's phenomenon; *RCT,* randomised-controlled trial; *mRSS,* modified Rodman skin score; *PFTs,* pulmonary function tests; *FVC,* forced vital capacity; *HAQ,* health assessment questionnaire; *DAS28,* disease activity score at 28 joints; *DLco,* diffusing capacity of carbon monoxide; *PBP,* peripheral blood perfusion; *DU,* digital ulcer; *RP,* Raynaud's phenomenon; *6MWD* 6-min walking distance; *NYHA class,* New York Heart Association Functional Classification of Heart Failure; *FMD,* flow-mediated dilatation; *RV mass,* right ventricular mass; *PVR,* pulmonary vascular resistance; *N/A,* not applicable/specified.

Table 1. Clinical studies of targeted therapies in systemic sclerosis published during the last 10 years.

2.1. Fibrosis

2.1.1. TGF-β pathway inhibitors

Central to the fibroblast-mediated overproduction of extracellular matrix and perturbed tissue repair in SSc are a number of pro-fibrotic growth factors, the most notable of which is transforming growth factor-β (TGF-β). The TGF-β pathway has been strongly implicated in the pathogenesis of systemic sclerosis in numerous *in vitro* and *in vivo* studies. One such example is the reduction in fibrosis seen in mouse models following the abrogation of TGF-β signalling [33, 34]. As such, the TGF-β pathway has been the focus of a number of studies in the search for targeted therapies for SSc, with several different approaches tested.

A logical approach is to target the growth factors themselves using neutralising antibodies. One of the first anti-TGF-β antibodies to be trialled in SSc was CAT-192, a recombinant human antibody against the TGF-β1 isoform. In Denton et al.'s pioneering study, CAT-192 was administered at different doses to a cohort of patients with early dcSSc using a randomised, double-blind, placebo-controlled study design [35]. Of the 45 patients enrolled into the study, 31 patients completed the trial. Four patients who received CAT-192 died during the study, although these deaths were thought to be a consequence of the underlying disease as opposed

to a direct result of treatment with CAT-192. Skin sclerosis scores, as determined by the modified Rodman skin score (mRSS), did not demonstrate any significant treatment effect for CAT-192, with a global improvement in mRSS occurring independently of CAT-192 treatment. Similarly, no significant differences were noted in pulmonary function or functional status, as determined by the Scleroderma Health Assessment Questionnaire (HAQ). Furthermore, an excess of adverse events and severe adverse events was noted in the CAT-192 treatment group, although the majority were thought not to be related to treatment.

As noted by Denton et al., the lack of efficacy shown by CAT-192 could possibly be explained by its relatively weak affinity for only one isoform of TGF-β ligand. They suggest that abrogation of all active isoforms of the TGF-β ligand might induce a greater anti-fibrotic effect, as demonstrated in animal models [35]. Importantly, however, the desire to abrogate pro-fibrotic pathways must be balanced against the loss of their normal physiological functions, including potential tumour-suppressant roles [36].

Fresolimumab is a neutralising antibody targeting all three isoforms of TGF-β. Rice et al. conducted an open-label pilot study of fresolimumab in 15 patients with early dcSSc, employing two different dosing schedules [37]. mRSS values were shown to improve significantly by 3 weeks ($p = 0.0002$), with the changes remaining significant at 17 weeks ($p = 0.0024$). The clinical improvements in skin thickness paralleled a decrease in the expression of TGF-β-related biomarkers in skin biopsies following fresolimumab treatment. Interestingly, by 24 weeks, the subjects' skin scores had begun to deteriorate, along with re-expression of the TGF-β-mediated biomarkers, suggesting progression of the underlying skin disease. This led the authors to question whether a longer course of treatment, or repeated treatments, might help to sustain the treatment response. This must be balanced against adverse treatment effects, however. Anaemia was the most commonly reported adverse event in the study, with 67% of subjects experiencing a decrease in haemoglobin levels of >10% from baseline. Bleeding from sites including the gastrointestinal tract, gums, eyes and nose was also reported in a number of patients.

Another anti-fibrotic agent thought to act, at least in part, by suppressing TGF-β signalling is pirfenidone. Pirfenidone is also thought to possess anti-inflammatory properties, with action against TNFα demonstrated in several studies [38, 39]. This dual anti-fibrotic and anti-inflammatory action makes pirfenidone an attractive candidate for use in SSc. Indeed, pirfenidone has been extensively studied in idiopathic pulmonary fibrosis, with several large phase III studies demonstrating improvements in progression-free survival [40, 41].

Khanna et al. recently studied pirfenidone in a 16-week, open-label study of 63 patients with SSc-associated interstitial lung disease (SSc-ILD) [42]. The primary aim of the study was to test pirfenidone's safety and tolerability in such patients. The vast majority of subjects did indeed experience adverse events during the course of the study, although most were mild or moderate in severity, with a similar adverse event profile to previous studies of pirfenidone in idiopathic pulmonary fibrosis. Median changes (from baseline) in the percentage of predicted forced vital capacity (FVC) and diffusing capacity of carbon monoxide (DLco) were non-significant, at -0.5% and +1.5%, respectively. Clinically insignificant changes in skin scores were also noted. Of note, the authors state clearly that this study was inadequately powered to assess efficacy.

Further studies are required before conclusions can be drawn on pirfenidone's efficacy in SSc. A case series of five patients with SSc-ILD treated with pirfenidone has provided hope of a potential benefit [43]. Vital capacity (as a percentage of predicted) was shown to improve by 12.2–28.9% in four patients following pirfenidone therapy, depending on the duration of follow-up. In the case of the fifth patient, vital capacity improved by a more modest 3.8% after pirfenidone therapy, albeit after only 3 months of follow-up. Furthermore, the authors noted that dyspnoea was attenuated in three patients, along with a reduction in ground-glass shadowing seen on the chest imaging of two patients. In another study of 12 patients, the potential benefits of topical pirfenidone in patients with localised scleroderma (morphoea) were demonstrated, with significant improvements seen in skin scores ($p = 0.002$) and histo-pathological markers ($p = 0.032$) at 6 months [44].

2.1.2. Tyrosine kinase inhibitors

Another approach is to target the downstream pathways induced by pro-fibrotic molecules such as TGF-β and platelet-derived growth factor (PDGF). The downstream pathways induced by these molecules require tyrosine kinase signalling [45]. Tyrosine kinase inhibitors are therefore strong candidates for use as anti-fibrotic agents in SSc. This is facilitated by the fact that several of these agents are already widely used in other conditions, such as in chronic myeloid leukaemia.

Pope et al. tested imatinib mesylate, an inhibitor of the BCR-ABL, c-kit and PDGF tyrosine kinase receptors, in a randomised, double-blind, placebo-controlled study of patients with active dcSSc over a 6-month period [45]. Outcomes measured included changes in skin scores, global assessments of patients' well-being and safety outcomes. Despite a plan to enrol 20 patients into the study, enrolment was cut short after 10 patients in view of the high observed number of adverse events. Side effects noted included diarrhoea, nausea, oedema and alopecia, with two patients requiring hospital admission. The tolerability remained poor despite a dose reduction from 200 mg twice daily to 200 mg once daily. Of the efficacy outcome measures assessed, no significant treatment effect was observed in skin scores or global assessment measures, although conclusions were limited by the small number of subjects and short study duration.

Focusing on SSC-associated lung fibrosis, Khanna et al. performed a 1-year, open-label study of imatinib in 20 SSc patients with active ILD [46]. Doses of up to 600 mg per day were used, with a mean dosage of 445 mg per day. In keeping with the outcome of Pope et al.'s study, 25% of subjects discontinued this study as a result of adverse events, with a similar profile of side effects noted. A modest, non-significant improvement in FVC was observed in patients receiving imatinib, coupled with a significant improvement in skin scores ($p < 0.001$). Further corroborating the results of this study, Spiera et al. demonstrated a significant improvement in skin scores ($p < 0.001$) and FVC ($p = 0.008$) in their open-label, 1-year study of imatinib 400 mg daily in 30 patients with dcSSc [47]. The improvements in skin scores seen in this study paralleled significant decreases in skin thickness as evident on skin biopsy ($p < 0.01$). Again, a large number of adverse events were noted in this study, with 171 adverse events thought to

be at least possibly related to imatinib. A 24-month open-label extension of this study demonstrated ongoing improvement in skin scores ($p = 0.002$) [48].

More recently, a phase II open-label study recruited 30 patients with active SSc-ILD, unresponsive to cyclophosphamide, and administered a lower dose of 200 mg daily of imatinib for 6 months [49]. Following an additional 6 months of follow-up, a range of respiratory outcome measures were assessed (with a 'good response' defined as an increase in FVC and/or DLco of >15%, combined with a PaO2 of >90% of the initial value and stable/improved lung imaging). Of the 26 subjects who completed the study, 4 subjects demonstrated a good response, 15 subjects had stable lung disease and 7 subjects had a worsening of their lung disease. Although fewer patients reached the criteria of 'good response' than their goal of 30%, the authors pointed out that their cohort of patients had advanced lung disease, unresponsive to conventional cyclophosphamide therapy. They suggested that a cohort of patients with earlier disease might experience greater benefit from imatinib therapy. Importantly, the lower dose of imatinib employed in this study was relatively well tolerated, with adverse events present in less than 20% of patients.

A second-generation tyrosine kinase inhibitor, nilotinib, was recently tested in an open-label pilot study of 10 patients with early dcSSc [50]. Nilotinib has been shown to have a favourable side-effect profile relative to imatinib when used in chronic myeloid leukaemia patients [50]. In the seven patients who completed the study, significant reductions were seen in skin scores after 6 months and 12 months of follow-up ($p = 0.02$ and 0.01, respectively). Significant improvements were also evident in the physician global assessment ($p = 0.0013$ at 12 months), although no significant differences were evident in measures of lung function. Seventy-one adverse events, including two serious adverse events, were reported in the study, with asymptomatic elevations in liver function tests and QTc prolongation being common adverse events.

2.1.3. Other agents

Another study employed a different approach when searching for novel targeted therapies for SSc [51]. Noting its proposed role as an autoantigen in SSc, the authors attempted to induce immune tolerance to type I collagen by administering it orally to 168 patients with dcSSc in a randomised, double-blind, placebo-controlled trial. In the primary efficacy outcome of mRSS, no significant differences were evident between the treated and placebo cohorts at 15 months. During subgroup analysis, the authors noted a significant reduction in mRSS in treated patients with late-phase disease ($p = 0.0063$), with the treatment effect first becoming apparent approximately 8 months after commencing treatment. Multiple adverse events were noted, although this was common to both the treated and placebo arms of the study.

Although named after its pregnancy-related functions, interest in recombinant human relaxin as a potential therapy for SSc stems from its ability to inhibit fibroblast-mediated collagen production and enhance collagen breakdown. A phase II, randomised, controlled study of recombinant human relaxin in patients with stable dcSSc demonstrated significant improvements in skin scores at 24 weeks, with evidence of benefit arising as early as 4 weeks into the follow-up period [52]. Following on from this study, Khanna et al. [53] performed a large phase

III study of relaxin at two doses in patients with dcSSc. Reductions in skin scores were noted in all groups, including placebo, with no significant differences between the study arms. No significant differences were evident in functional outcome measures and FVC deteriorated in patients receiving relaxin ($p < 0.04$). Furthermore, of the 36 subjects who dropped out of the study prematurely, 14 were as a result of adverse events, most notably of the renal system.

2.2. Inflammation

2.2.1. TNFα inhibitors

Given the success of TNFα inhibitors in other autoimmune rheumatological conditions, several studies have examined their use in SSc. Prior studies had shown that TNFα counters extracellular matrix production by fibroblasts *in vitro*, leading to concerns that TNFα inhibitors might potentiate fibrosis in SSc [54, 55]. This contrasted the results of several animal studies, where TNFα abrogation resulted in reductions in fibrosis [54, 56, 57]. It has been proposed that the effect of TNFα inhibition in SSc might vary depending on the stage of the disease. During the early inflammation-predominant phases of SSc, TNFα inhibitor-mediated suppression of inflammation may lead to a reduction in subsequent fibrosis, as seen in animal studies. This is supported by the enhanced expression of TNFα in leucocytes from patients with early SSc [58]. During the later fibrosis-predominant stages of SSc, TNFα inhibitor-mediated suppression of inflammation is less likely to be of significance and may even be pro-fibrotic in nature, as suggested by *in vitro* studies [54, 59].

Lam et al. conducted a retrospective analysis of 18 patients with scleroderma-associated joint disease who had been treated with etanercept, a decoy receptor that binds to circulating TNFα [60]. Concurrent treatment with other disease-modifying agents or corticosteroids was permitted in their analysis. Eighty-three percent of patients demonstrated a positive response to etanercept therapy, as determined by the treating physician on follow-up review. Mean HAQ scores and skin scores showed non-significant trends towards improvement ($p = 0.13$ and 0.12, respectively). Pulmonary function readings deteriorated during the course of etanercept therapy, albeit to a small degree, in keeping with the gradual decline in lung function seen in patients who did not receive etanercept therapy.

Infliximab, a chimaeric monoclonal antibody against TNFα, has also been tested in an open-label study of 16 patients with dcSSc [61]. In addition to a number of clinical outcome measures, several histopathological and serum correlates of collagen synthesis were measured. No significant difference was noted in skin scores at the 26-week end point, although a non-significant trend towards a lower mRSS was evident at 22 weeks ($p = 0.10$). Significant reductions were evident in the degree of type I collagen synthesis by dermal fibroblasts at 26 weeks ($p = 0.02$) and in the serum levels of aminoterminal propeptide of type III collagen ($p = 0.03$). Of the 127 adverse events that occurred during the course of the study, 19 adverse events were thought to be attributable to infliximab, with half of the patients prematurely discontinuing the therapy.

Following on from these studies, a multi-centre, retrospective analysis of TNFα inhibitor use in SSc was performed by the EULAR Scleroderma Trials and Research (EUSTAR) group [54].

Sixty-five patients who had received an anti-TNFα agent during the course of their treatment (most commonly infliximab and etanercept) were identified. Of the 65 patients analysed, 48 had shown evidence of improvement, with the majority of benefit seen in patients with joint-related symptoms. Improvements in fibrosis were less convincing, with six patients experiencing an improvement in fibrosis and seven patients experiencing a worsening of fibrosis. Using the Delphi technique to reach an expert consensus, 50% of centres ultimately recommended against using TNFα inhibitors in SSc other than in the setting of clinical trials, 9% of centres advised against their use entirely, and 38% of centres advocated consideration of TNFα inhibitors in SSc-associated joint disease.

2.2.2. Selective co-stimulation modulators

Abatacept is a fusion protein comprising the extracellular domain of human cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and the modified Fc portion of human immuno-globulin G1 [62]. It is licensed as a treatment for moderate-to-severe rheumatoid arthritis that has failed to respond to conventional immunosuppressant therapy, and has been shown to have comparable efficacy to TNFα inhibitors [11, 63–65]. By binding to CD80/CD86 on the surface of antigen-presenting cells, abatacept inhibits the co-stimulatory interactions required for the activation of T-cells. T-cells have been strongly implicated in the pathogenesis of SSc and, as such, a number of studies have investigated the role of abatacept as a treatment for SSc [66, 67].

In a double-blind, placebo-controlled study, seven patients were randomised to receive abatacept and compared to three control patients [67]. Although limited by the small number of subjects, a trend towards improvement in absolute skin scores was noted with abatacept therapy at the 24-week end point ($p = 0.0625$). This improvement became statistically significant when the differences in disease duration between the two cohorts were accounted for ($p = 0.0114$). Patients receiving abatacept therapy also noted greater improvements in HAQ and visual analogue scores. Abatacept therapy was well tolerated, with no serious adverse events noted during the course of the study.

The EUSTAR group's observational study of two separate biological therapies—abatacept and tocilizumab (see below)—provides evidence to support abatacept's use in a cohort of patients with SSc-associated refractory arthritis [68]. Of the patients with joint disease receiving abatacept therapy, 6/11 reached the EULAR-specified criteria for a good response in their 28-joint count Disease Activity Score at 11 months. More impressive still was the 10/15 patients who achieved a good response in their joint scores following tocilizumab therapy after 5 months of follow-up. No benefit was seen in myopathic patients receiving abatacept therapy or in skin or lung fibrosis with either abatacept or tocilizumab therapy.

2.2.3. IL-2α inhibitors

Basiliximab, a chimaeric monoclonal antibody against CD25, disrupts T-cell action via a different mechanism to abatacept. The CD25 antigen corresponds to the alpha chain of the interleukin-2 (IL-2α) receptor, a transmembrane protein expressed on the surface of activated

T-cells [69]. By competing with IL-2 for access to its receptor, basiliximab disrupts the down-stream effects of activated T-cells. Basiliximab has been utilised successfully as part of immu-nosuppressive regimens to prevent the acute rejection of transplanted organs [70]. The promising results of a phase II study of basiliximab in patients with skin fibrosis resulting from acute graft-versus-host disease also support its potential as a therapy for SSc [71].

Basiliximab was tested in an open-label, prospective study of 10 patients with rapidly pro-gressive SSc [72]. As well as being relatively well tolerated, basiliximab therapy resulted in a significant improvement in skin scores by week 68 of follow-up ($p = 0.015$). A trend towards an improvement in mean FVC was also noted by week 44 ($p = 0.078$). Given the small size and open-label nature of this study, further trials are necessary before definitive comments can be made about basiliximab's efficacy in SSc. However, the results of this pilot study support the beneficial response seen in a case study of a patient with recalcitrant SSc, who responded favourably to basiliximab, in conjunction with cyclophosphamide [73].

2.2.4. IL-6 inhibitors

Tocilizumab is a humanised monoclonal antibody targeting the interleukin-6 (IL-6) receptor. As with abatacept and TNFα inhibitors, tocilizumab is an effective treatment for moderate-to-severe rheumatoid arthritis which has failed to respond adequately to conventional disease-modifying agents. In addition to its pro-inflammatory effects, IL-6 has been shown to be pro-fibrotic, as well as an endothelial cell activator [74, 75]. IL-6 levels are elevated in the serum of patients with dcSSc and predict poorer long-term clinical outcomes [75, 76].

Following on from the observational study of tocilizumab and abatacept in patients with SSc-associated joint disease (mentioned above), a case series published by Fernandes das Neves et al. demonstrated evidence of clinical improvement in three treatment-refractory SSc patients treated with tocilizumab [68, 77]. More recently, the safety and efficacy of tocilizumab in SSc was studied in a phase II, double-blind, randomised, placebo-controlled trial of 87 patients with a disease duration of less than 5 years [78]. A trend towards improvement was evident in the primary outcome (mean change in mRSS); however, this did not reach statistical significance at 48 weeks ($p = 0.0579$). No significant difference was evident in clinical symptoms or in global disease severity scores. However, significantly fewer patients in the tocilizumab cohort experienced a decline in FVC at 48 weeks ($p = 0.0373$). A relatively large number of patients in both cohorts experienced severe adverse events (33% treatment vs. 34% placebo), with a greater number of serious infections noted in the tocilizumab cohort and one death as a result of tocilizumab therapy. Further information about tocilizumab's efficacy and safety in SSc will be provided by the ongoing phase III study [79].

2.2.5. B-cell depletion

Rituximab is a chimaeric monoclonal antibody that targets the CD20 antigen, resulting in the depletion of peripheral B-cells. It has been shown to be highly effective in the treatment of rheumatoid arthritis, where it is often used as a rescue therapy for patients with refractory disease. Rituximab's clinical efficacy has to be weighed against the potential for serious side

effects, which include infusion reactions, predisposition to infection and hypogammaglobulinaemia, and the serious but infrequent complication of progressive multifocal leukoencephalopathy.

A body of evidence supporting the role of B-cells in the pathogenesis of SSc has spurred interest in rituximab as a therapy for SSc. Indeed, B-cell depletion has been shown to suppress skin fibrosis and autoantibody production in mouse models of SSc, when utilised in early stages of the disease [80, 81]. An early, open-label, pilot study of rituximab in 15 patients with dcSSc produced disappointing results, however [82]. Although relatively safe and well tolerated, rituximab therapy failed to produce a significant improvement in skin scores after 6 and 12 months of follow-up ($p = 0.82$ and 0.83, respectively). This was despite demonstrable depletion of B-cells in the periphery and dermis. This pilot study has been followed by a number of studies which support the role of rituximab therapy in SSc [83–90].

In a 1-year prospective study by Daoussis et al., eight patients with SSc were randomised to receive two cycles of rituximab therapy, in addition to standard treatment, and compared to six patients who received standard treatment alone [87]. Relative to baseline, FVC improved significantly with rituximab therapy at the 1-year end point, with a median improvement of 10% ($p = 0.0018$). This was significantly improved relative to controls, where a median decline in FVC of 5% was evident ($p = 0.002$). Significant improvements were also evident in DLco and skin scores in the rituximab cohort ($p = 0.017$ and $p < 0.001$, respectively). An open-label extension of this study, whereby a further two cycles of rituximab therapy were administered, demonstrated ongoing improvements in FVC, DLco and skin scores at 2 years [88].

A 2-year, open-label, prospective study by Smith et al. [89] provided further evidence of rituximab's efficacy in SSc. Following two cycles of rituximab in eight patients with early dcSSc, statistically significant reductions in skin scores, disease activity scores and biomarkers of collagen deposition were evident by the 24-month end point ($p < 0.0001$, $p < 0.0001$ and $p = 0.009$, respectively). The EUSTAR group employed a retrospective case-control analysis to collate evidence on rituximab use in SSc across a number of centres [81]. Sixty-three patients were identified who had received rituximab during the course of their treatment. Several outcome measures were compared retrospectively to patients with SSc who had not received rituximab therapy. In patients treated with rituximab, mean skin scores were found to be significantly lower than baseline after a period of follow-up ($p = 0.0001$). In the subset of patients with severe dcSSc receiving rituximab, reductions in skin scores were significantly greater than matched controls ($p = 0.03$). Furthermore, patients with SSc-associated ILD experienced a stabilisation in their FVC following rituximab therapy, relative to matched controls ($p = 0.02$).

More recently, an open-label, prospective study of 30 SSc patients from three centres added further weight to the evidence base supporting rituximab's use in SSc [90]. Patients received four cycles of rituximab therapy over 18 months, followed by consideration for further cycles by their treating physician. After 1 and 2 years of follow-up, FVC had significantly improved relative to baseline ($p < 0.001$ and $p = 0.018$, respectively), with the same being true of DLco at 2 years ($P = 0.012$). By 5 years, FVC was shown to have stabilised ($p = 0.05$). Skin scores also improved significantly at all time points ($P < 0.001$). Again, rituximab was reported as being relatively well tolerated in this study.

Using a different approach, Schiopu et al. utilised a humanised anti-CD19 monoclonal antibody (MEDI-551) to deplete B-cells [91]. As noted by the authors, the CD19 antigen is expressed on a wider range of B-cell subsets than the CD20 antigen. In their study, 24 subjects were randomised to receive a single dose of MEDI-551 and compared to four subjects who received placebo therapy. The primary aim of the study was to test MEDI-551's safety and tolerability in SSc subjects. An excess of adverse events was indeed noted in the treatment cohort (95.8% of subjects) relative to the placebo cohort (75% of subjects), with the majority being mild or moderate events. Of the serious adverse events, two were thought possibly to have been a consequence of MEDI-551 treatment. Given that a number of studies of rituximab demonstrate the probable benefits of more prolonged B-cell depletion in SSc, this 85-day study of MEDI-551 was limited in its ability to discern clinical efficacy. A trend towards improvement in skin scores with MEDI-551 treatment was noted relative to placebo, although no clear evidence of benefit was seen in pulmonary function tests. Further studies are needed to determine its efficacy more conclusively.

2.2.6. Type I IFN receptor antagonists

Using another targeted approach to developing novel therapies for SSc, Goldberg et al. tested MEDI-546, a monoclonal antibody against the type I interferon (IFN) receptor, in patients with SSc [92]. Case reports have documented incident systemic sclerosis arising in patients who had previously received IFNα therapy for chronic viral hepatitis [93, 94]. An activated type I IFN profile and gene signature are present in patients with SSc and administration of MEDI-546 not only reduces serum levels of several IFN-induced proteins but also suppresses levels of markers of extracellular matrix turnover and TGF-β signalling [95, 96].

In a study designed to test MEDI-546's safety and tolerability in SSc, rather than its efficacy, Goldberg et al. administered the treatment to 34 subjects and recorded a range of safety, pharmacokinetic and immunogenicity outcomes after 12 weeks of follow-up [92]. Of the 148 adverse events, four were recorded as serious adverse events, one of which was a new diagnosis of chronic myelogenous leukaemia occurring after 10 months. Phase II, placebo-controlled studies are necessary before MEDI-546's efficacy in SSc can be commented on. Indeed, phase II studies of MEDI-546 are already ongoing in systemic lupus erythematosus (SLE).

2.3. Vascular

2.3.1. Endothelin receptor antagonists

The vasculopathy seen in SSc is characterised by endothelial cell damage and dysfunction and fibrotic obliteration of the vasculature, with consequent ischaemia-reperfusion injury [97]. This, in turn, stimulates the production of the potent vasoconstrictor, endothelin, which has been strongly implicated as a mediator of vascular injury in SSc. The vascular manifestations that result from these pathogenic processes include Raynaud's phenomenon (RP) and digital ulceration, pulmonary arterial hypertension (PAH) and renal crises.

One of few licensed targeted therapies for SSc is bosentan. Bosentan disrupts the endothelin-signalling axis by antagonising both of its receptors, endothelin-A and endothelin-B. Bosentan has been shown in a large number of studies to be an effective treatment for PAH, including SSc-associated PAH (SSc-PAH). Its use leads to improvements in symptoms, exercise capacity and a range of haemodynamic values [98, 99]. Several studies have also investigated bosentan's efficacy for the other vascular manifestations of SSc, most notably RP and digital ulceration, details of which are given below.

The RAPIDS-2 study was a large randomised, placebo-controlled trial designed to evaluate bosentan's efficacy in the treatment of SSc-associated digital ulcers. One hundred and eighty-eight patients with SSc and active digital ulcers were recruited from a number of centres, of which 98 were administered bosentan over the course of 20 weeks [100]. At the 24-week end point, a 30% reduction in the number of new digital ulcers was evident in the cohort receiving bosentan ($p = 0.04$). No significant difference was evident in ulcer healing time, however. The beneficial effects of bosentan on reducing digital ulcer formation are supported by two further studies—a retrospective analysis of 67 patients and a 3-year prospective, open-label study [101, 102]. Although generally well tolerated, all three studies demonstrated bosentan's well-documented side effect of inducing liver dysfunction. This is reversible in the vast majority of cases, although close monitoring of liver function during therapy is essential. This is high-lighted by the results of a small study of bosentan in patients with SSc-associated digital ulcers, during which 50% of patients had to discontinue bosentan due to severe liver dysfunction [103].

It has been proposed that the differential effects of bosentan on digital ulcer formation and healing might stem from various pro- and anti-vasoconstrictive effects of the medication [104]. Ambrisentan also targets the endothelin axis but does so by selectively antagonising the endothelin-A receptor, as opposed to the dual-receptor blockade mediated by bosentan. The effects of ambrisentan on SSc-associated digital ulcer number and healing were analysed in a prospective, open-label study of 20 patients [104]. A significant decrease in the number of digital ulcers per patient was noted at 24 weeks relative to baseline ($p < 0.004$). The maximum diameter of patients' digital ulcers was also noted to decrease ($p < 0.0001$), and 88% of patients who completed the study had full resolution of all their baseline digital ulcers. Importantly, no study subjects developed deranged liver function tests during the course of this study.

The efficacy of ambrisentan in patients with SSc-PAH has also been tested in a prospective, open-label study [105]. Twenty-four patients with treatment-naïve SSc-PAH were adminis-tered dual therapy with ambrisentan and tadalafil, a phosphodiesterase type-5 inhibitor, for 36 weeks. Following this course of treatment, significant reductions were noted in pulmonary vascular resistance ($p < 0.0001$) and right ventricular mass ($p < 0.05$), as well as improvements in 6-min walk distances ($p = 0.001$) and other haemodynamic and structural outcome measures. These results are supported by those of another study, in which 12 patients with SSc-associated exercise-induced PAH experienced significant improvements in exercise-pulmonary vascular resistance and 6-min walk distances following 24 weeks of treatment with ambrisentan ($p = 0.004$ and 0.003, respectively) [106].

Ambrisentan has also been shown to reduce the incidence of SSc-associated Raynaud's phenomenon (SSc-RP) attacks, albeit it in a study of only six patients ($p = 0.01$) [107]. Bosentan's

effect on SSc-RP has been more extensively studied, with mixed results. In a retrospective analysis of 14 patients, bosentan use was associated with a significant decrease in the number and duration of RP attacks ($p < 0.05$) [97]. An open-label prospective study of 15 patients with lcSSc-associated RP also demonstrated a significant reduction in the duration, frequency and intensity of RP attacks with bosentan use ($p < 0.05$) [108]. These findings contrast the results of a randomised, placebo-controlled study involving 16 subjects with SSc-RP (without pre-existing digital ulcers). Relative to placebo, no improvements in the duration, intensity or frequency of RP attacks were seen with bosentan use, despite improvements in functional scores.

In addition to endothelin's prominent role as a mediator of vascular injury in SSc, it has also been implicated in promoting fibrosis. *In vitro*, endothelin stimulates production and deposition of extracellular matrix by fibroblasts, as well as facilitating the pro-fibrotic properties of TGF-β [97, 109, 110]. Endothelin levels are also elevated in the serum and bronchoalveolar lavage fluid of patients with SSc-ILD [111]. In light of endothelin's reported pro-fibrotic roles, the effects of bosentan on SSc-associated skin and lung fibrosis have been tested in a number of studies.

In a prospective, placebo-controlled study of patients with SSc-ILD, 77 patients were randomised to receive bosentan and their 6-min walk distances and oxygen saturations compared to 86 controls [112]. At 12 months, no significant difference was evident in walking distances between the study cohorts ($p = 0.404$), with the same being true of pulmonary function test results. Furuya et al. also examined bosentan's use in SSc-ILD in a 24-month open-label trial of 9 patients who were deemed ineligible for cyclophosphamide therapy [113]. Of the 7 patients who completed the study, a trend towards improvement in FVC, DLco and total lung capacity was noted. This contrasted the findings on high-resolution computed tomography (CT) thorax scans, which showed a gradual progression of the underlying fibrosis. Moreover, no benefit on cumulative survival was evident when the subjects were compared to historical controls.

Bosentan's effect on skin fibrosis was evaluated in a retrospective, open-label study of 14 patients who were receiving bosentan for SSc-PAH [97]. As well as noting reductions in the duration and number of RP attacks, significant reductions in skin scores were present in the study cohort after 24 weeks of follow-up ($p < 0.01$). The retrospective nature of this study and the lack of control subjects both necessitate a degree of caution when interpreting these results, particularly as spontaneous regression of skin disease is not uncommonly seen in SSc patients. Indeed, Seibold et al.'s placebo-controlled study of bosentan in SSc-ILD (described above) failed to show any significant treatment effect on skin thickness scores. This contrasts the results of another, albeit much smaller, prospective study which did highlight a significant improvement in mRSS with bosentan therapy ($p < 0.001$) [114]. Again, the lack of control subjects in this study makes it difficult to separate bosentan's effects on skin scores from the improvements sometimes seen in the natural progression of SSc.

Another endothelin-receptor antagonist to have been studied in SSc is macitentan. Like bosentan, macitentan acts to antagonise both of the endothelin receptors, albeit with a much greater affinity for the endothelin-A receptor. Macitentan's effects on SSc-associated digital ulcers were recently studied in two phase III placebo-controlled trials with a total of 554 study

subjects [115]. After 16 weeks of follow-up, no significant treatment effect was evident in the primary end point of cumulative number of new digital ulcers. The same was true of the secondary end points of digital ulcer healing, total ulcer burden and hand function.

2.3.2. Other agents

Two other targeted vascular therapies worthy of mention are fasudil and ORM-12741, both of which have primary targets outside of the endothelin axis. Fasudil is a RhoA/Rho kinase inhibitor that abrogates the α2C-adrenoceptor-mediated response to cold exposure, whereas ORM-12741 acts as a direct α2C-adrenoceptor antagonist. When studied in patients with SSc-associated RP, neither agent enhanced recovery in blood flow nor skin temperature following cold challenges [116, 117]. Although unsuccessful in their trials to date, fasudil and ORM-12741 provide us with further examples of how research into the pathogenesis of SSc can be translated into novel candidates for drug therapies.

3. Conclusion

In this chapter, we have reviewed a wide range of targeted therapies for SSc. Our systematic literature search identified 69 clinical studies of targeted therapies with diverse modes of action. This reflects the concerted efforts of clinicians and researchers trying to identify novel therapies for this disabling condition.

Progress has already been made in improving the outlook for certain groups of patients with SSc. Autologous haematopoietic stem cell transplantation, for example, has been shown to benefit patients with early, aggressive dcSSc. Unfortunately, this benefit comes at the expense of significant treatment-related morbidity and mortality, thereby limiting the utility of this treatment for the majority of patients with SSc.

The discovery of efficacious targeted therapies has the potential to transform the outlook for patients with SSc, just as TNFα inhibitors have done in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. In this regard, most progress has been made in developing targeted therapies for the vascular manifestations of SSc. The endothelin-receptor antagonists bosentan and ambrisentan have been tested in more than 30 clinical studies involving patients with SSc. As detailed above, many of these studies have demonstrated statistically significant treatment effects on vascular manifestations such as PAH and digital ulcer formation. A phase II study of zibotentan, a selective endothelin-receptor A antagonist, is also currently underway for patients with SSc-associated renal dysfunction [118].

Improvements in our understanding of another of the central pillars of SSc pathogenesis – fibrosis – have also been made. The studies of the anti-TGF-β antibodies, CAT-192 and fresolimumab, are excellent examples of how an understanding of the pathogenic processes underlying SSc can be translated into targeted therapies. The improvements seen in skin fibrosis scores following treatment with fresolimumab provide us with an exciting glimpse of the potential benefits of targeted anti-fibrotic therapies. This excitement is partly tempered by

the large number of adverse events seen in this study; a clear reminder of the potential pitfalls of disturbing physiological functions, such as fibrosis and healing.

Of the targeted anti-inflammatory therapies, a great deal of optimism can be derived from the studies of rituximab, a B-cell-depleting antibody with efficacy in a wide range of clinical conditions. Of the 10 studies identified that assessed rituximab in SSc, 9 demonstrated statistically significant treatment effects. Moreover, 6 of these studies revealed treatment benefits in measures of both skin and lung fibrosis. Rituximab also provides us with an example of how an existing targeted therapy can be adopted for use in SSc. Analysis of safety and efficacy data from studies in other conditions can help tailor the design of studies of rituximab in SSc and expedite the transition process.

As demonstrated in **Table 1**, a large number of the trials involving targeted therapies in SSc have been small, open-label studies. Their limited size and, in many cases, lack of control subjects reduces the reliability of their outcome data. Large randomised, placebo-controlled studies are essential before definitive conclusions can be drawn about a particular treatment. Performing such studies in SSc is challenging given the rarity of the condition and the heterogeneity in its presentation and natural progression. Multi-centre collaboration can help to overcome these barriers by increasing the pool of subjects available for trials. Indeed, multi-centre randomised, controlled trials have already been performed for bosentan, macitentan, tocilizumab, MEDI-551, relaxin, oral type-I collagen, CAT-192 and imatinib mesylate. A number of large randomised, placebo-controlled trials are also ongoing for several of the therapies covered in this chapter. Examples include the ASSET trial—a phase II study of abatacept's efficacy in dcSSc—and the focuSSced trial—a phase III study of tocilizumab in SSc [79, 119].

A better understanding of the pathogenic processes underlying SSc will help to reduce the heterogeneity of study cohorts in trials of SSc. Stratification of patients into cohorts with specific biochemical or clinical characteristics will permit tailoring of treatments to those patients most likely to benefit. For example, an anti-cytokine therapy might be offered to those patients with a cytokine profile that suggests they are likely to benefit from such a therapy.

An improved understanding of the pathogenic processes underlying SSc will also increase the number of available drug targets. Trials are currently underway for a number of agents with novel mechanisms of action. The pan-peroxisome proliferator-activated receptor (PPAR) agonist, IVA337, is currently being investigated in a phase II randomised, controlled study of patients with dcSSc [120]. The anti-fibrotic properties of PPAR agonists are supported by the results of a recent study in a mouse model of dermal fibrosis, in which IVA337 administration produced reductions in extracellular matrix deposition and several biomarkers of inflammation and fibrosis [121]. Also promising is the ongoing phase III study of nintedanib in patients with SSc-ILD [122]. Nintedanib is a tyrosine kinase inhibitor that targets the receptors of vascular endothelial growth factor, fibroblast growth factor and PDGF. It has been shown to retard the progression of idiopathic pulmonary fibrosis in phase III studies and reduce fibrosis in multiple mouse models of SSc [123, 124]. Another candidate therapy worthy of mention is riociguat, a soluble guanylate cyclase stimulator that possesses both vasodilatory and anti-fibrotic properties. Riociguat has been shown to improve exercise ca-

pacity and several other haemodynamic and functional outcomes in patients with symptomatic PAH, and its effects on measures of skin and lung fibrosis are currently being assessed in a phase II study of patients with dcSSc [125].

Author details

Mark D. Russell[*] and Nidhi Sofat

*Address all correspondence to: mdrussell@doctors.org.uk

Institute of Infection and Immunity, St George's, University of London, United Kingdom

References

[1] Buchan G, Barrett K, Turner M, et al. Interleukin-1 and tumour necrosis factor mRNA expression in rheumatoid arthritis: Prolonged production of IL-1 alpha. Clinical and Experimental Immunology. 1988;73(3):449–55.

[2] Chu CQ, Field M, Feldmann M, et al. Localization of tumor necrosis factor alpha in synovial tissues and at the cartilage-pannus junction in patients with rheumatoid arthritis. Arthritis and Rheumatism. 1991;34(9):1125–32.

[3] Williams RO, Feldmann M, Maini RN. Anti-tumor necrosis factor ameliorates joint disease in murine collagen-induced arthritis. Proceedings of the National Academy of Sciences of the United States of America. 1992;89(20):9784–8.

[4] Elliott MJ, Maini RN, Feldmann M, et al. Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor alpha. Arthritis and Rheumatism. 1993;36(12):1681–90.

[5] Elliott MJ, Maini RN, Feldmann M, et al. Repeated therapy with monoclonal antibody to tumour necrosis factor alpha (cA2) in patients with rheumatoid arthritis. Lancet. 1994;344(8930):1125–7.

[6] Elliott MJ, Maini RN, Feldmann M, et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. Lancet. 1994;344(8930):1105–10.

[7] NICE. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis [Internet]. 2007. Available at: http://www.nice.org.uk/TA130 (Accessed: 27 September 2016).

[8] NICE. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor [Internet]. 2010. Available from: http://www.nice.org.uk/TA195 (Accessed: 27 September 2016).

[9] Nam JL, Ramiro S, Gaujoux-Viala C, et al. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2013 update of the EULAR recommendations for the management of rheumatoid arthritis. Annals of the Rheumatic Diseases. 2014;73(3):516–28. doi: 10.1136/annrheumdis-2013-204577

[10] Williams RO, Paleolog E, Feldmann M. Cytokine inhibitors in rheumatoid arthritis and other autoimmune diseases. Current Opinion in Pharmacology. 2007;7(4):412–7. doi: 10.1016/j.coph.2007.06.001

[11] NICE. Abatacept for treating rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs [Internet]. 2013. Available at: http://www.nice.org.uk/TA280 (Accessed: 27 September 2016).

[12] NICE. Tocilizumab for the treatment of rheumatoid arthritis [Internet]. 2012. Available at: http://www.nice.org.uk/TA247 (Accessed: 27 September 2016).

[13] NICE. Rheumatoid arthritis in adults: Management [Internet]. 2009. Available at: http://www.nice.org.uk/CG79 (Accessed: 27 September 2016).

[14] NICE. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis [Internet]. 2010. Available at: http://www.nice.org.uk/TA199 (Accessed: 27 September 2016).

[15] NICE. Adalimumab, etanercept and infliximab for ankylosing spondylitis [Internet]. 2008. Available at: http://www.nice.org.uk/TA143 (Accessed: 27 September 2016).

[16] NICE. Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis [Internet]. 2015. Available at: http://www.nice.org.uk/TA373 (Accessed: 27 September 2016).

[17] NICE. Infliximab and adalimumab for the treatment of Crohn's disease [Internet]. 2010. Available at: http://www.nice.org.uk/TA187 (Accessed: 27 September 2016).

[18] NICE. Ustekinumab for treating active psoriatic arthritis [Internet]. 2015. Available at: http://www.nice.org.uk/TA340 (Accessed: 27 September 2016).

[19] NICE. Secukinumab for treating moderate to severe plaque psoriasis [Internet]. 2015. Available at: http://www.nice.org.uk/TA350 (Accessed: 27 September 2016).

[20] McInnes IB, Mease PJ, Kirkham B, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015;386(9999):1137–46. doi: 10.1016/S0140-6736(15)61134-5

[21] NICE. Belimumab for treating active autoantibody-positive systemic lupus erythema-tosus [Internet]. 2016. Available at: https://www.nice.org.uk/guidance/TA397 (Accessed: 72 September 2016).

[22] Denton CP, Black CM, Abraham DJ. Mechanisms and consequences of fibrosis in systemic sclerosis. Nature Clinical Practice Rheumatology. 2006;2(3):134–44. doi: 10.1038/ncprheum0115

[23] Kowal-Bielecka O, Landewé R, Avouac J, et al. EULAR recommendations for the treatment of systemic sclerosis: A report from the EULAR Scleroderma trials and research group (EUSTAR). Annals of the Rheumatic Diseases. 2009;68(5):620–8. doi: 10.1136/ard.2008.096677

[24] Denton CP, Hughes M, Gak N, et al. BSR and BHPR guideline for the treatment of systemic sclerosis. Rheumatology (Oxford). 2016;55(10):1906–10. doi: 10.1093/rheumatology/kew224

[25] Denton CP. Systemic sclerosis: from pathogenesis to targeted therapy. Clinical and Experimental Rheumatology. 2015;33(4 Suppl 92):S3–7.

[26] van Laar JM, Farge D, Sont JK, et al. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. JAMA. 2014;311(24):2490–8. doi: 10.1001/jama.2014.6368

[27] Burt RK, Shah SJ, Dill K, et al. Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial. Lancet. 2011;378(9790):498–506. doi: 10.1016/S0140-6736(11)60982-3

[28] Poelman CL, Hummers LK, Wigley FM, et al. Intravenous immunoglobulin may be an effective therapy for refractory, active diffuse cutaneous systemic sclerosis. The Journal of Rheumatology. 2014;42(2):236–42. doi: 10.3899/jrheum.140833

[29] Takehara K, Ihn H, Sato S. A randomized, double-blind, placebo-controlled trial: intravenous immunoglobulin treatment in patients with diffuse cutaneous systemic sclerosis. Clinical and Experimental Rheumatology. 2013;31(2 Suppl 76):151–6.

[30] Raja J, Nihtyanova SI, Murray CD, et al. Sustained benefit from intravenous immunoglobulin therapy for gastrointestinal involvement in systemic sclerosis. Rheumatology (Oxford). 2016;55(1):115–9. doi: 10.1093/rheumatology/kev318

[31] Nacci F, Righi A, Conforti ML, et al. Intravenous immunoglobulins improve the function and ameliorate joint involvement in systemic sclerosis: a pilot study. Annals of the Rheumatic Diseases. 2007;66(7):977–9. doi: 10.1136/ard.2006.060111

[32] Denton CP, Ong VH. Targeted therapies for systemic sclerosis. Nature Reviews Rheumatology. 2013;9(8):451–64. doi: 10.1038/nrrheum.2013.46

[33] McCormick LL, Zhang Y, Tootell E, et al. Anti-TGF-beta treatment prevents skin and lung fibrosis in murine sclerodermatous graft-versus-host disease: a model for human scleroderma. Journal of Immunology. 1999;163(10):5693–9.

[34] Ruzek MC, Jha S, Ledbetter S, et al. A modified model of graft-versus-host-induced systemic sclerosis (scleroderma) exhibits all major aspects of the human disease. Arthritis and Rheumatism. 2004;50(4):1319–31. doi: 10.1002/art.20160

[35] Denton CP, Merkel PA, Furst DE, et al. Recombinant human anti-transforming growth factor beta1 antibody therapy in systemic sclerosis: a multicenter, randomized, placebo-controlled phase I/II trial of CAT-192. Arthritis and Rheumatism;56(1):323–33. doi: 10.1002/art.22289

[36] Elliott RL, Blobe GC. Role of transforming growth factor beta in human cancer. Journal of Clinical Oncology. 2005;23(9):2078–93. doi: 10.1200/JCO.2005.02.047

[37] Rice LM, Padilla CM, McLaughlin SR, et al. Fresolimumab treatment decreases biomarkers and improves clinical symptoms in systemic sclerosis patients. The Journal of Clinical Investigation. 2015;125(7):2795–807. doi: 10.1172/JCI77958

[38] Grattendick KJ, Nakashima JM, Feng L, et al. Effects of three anti-TNF-alpha drugs: etanercept, infliximab and pirfenidone on release of TNF-alpha in medium and TNF-alpha associated with the cell in vitro. International Immunopharmacology. 2008;8(5): 679–87. doi: 10.1016/j.intimp.2008.01.013

[39] Oku H, Nakazato H, Horikawa T, et al. Pirfenidone suppresses tumor necrosis factor-alpha, enhances interleukin-10 and protects mice from endotoxic shock. European Journal of Pharmacology. 2002;446:167–76.

[40] King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. The New England Journal of Medicine. 2014;370(22):2083–92. doi: 10.1056/NEJMoa1402582

[41] Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet. 2011;377(9779):1760–9. doi: 10.1016/S0140-6736(11)60405-4

[42] Khanna D, Albera C, Fischer A, et al. An open-label, phase II study of the safety and tolerability of Pirfenidone in patients with scleroderma-associated interstitial lung disease: the LOTUSS trial. The Journal of Rheumatology. 2016;43(9):1672–9. doi: 10.3899/jrheum.151322

[43] Miura Y, Saito T, Fujita K, et al. Clinical experience with pirfenidone in five patients with scleroderma-related interstitial lung disease. Sarcoidosis, Vasculitis and Diffuse Lung Diseases. 2014;31(3):235–8.

[44] Rodríguez-Castellanos M, Tlacuilo-Parra A, Sánchez-Enríquez S, et al. Pirfenidone gel in patients with localized scleroderma: a phase II study. Arthritis Research & Therapy. 2014;16(6):510. doi: 10.1186/s13075-014-0510-4

[45] Pope J, McBain D, Petrlich L, et al. Imatinib in active diffuse cutaneous systemic sclerosis: results of a six-month, randomized, double-blind, placebo-controlled, proof-

of-concept pilot study at a single center. Arthritis and Rheumatism. 2011;63(11):3547–51. doi: 10.1002/art.30549

[46] Khanna D, Saggar R, Mayes MD, et al. A one-year, phase I/IIa, open-label pilot trial of imatinib mesylate in the treatment of systemic sclerosis-associated active interstitial lung disease. Arthritis and Rheumatism. 2011;63(11):3540–6. doi: 10.1002/art.30548

[47] Spiera RF, Gordon JK, Mersten JN, et al. Imatinib mesylate (Gleevec) in the treatment of diffuse cutaneous systemic sclerosis: results of a 1-year, phase IIa, single-arm, open-label clinical trial. Annals of the Rheumatic Diseases. 2011;70(6):1003–9. doi: 10.1136/ard.2010.143974

[48] Gordon J, Udeh U, Doobay K, et al. Imatinib mesylate (Gleevec™) in the treatment of diffuse cutaneous systemic sclerosis: results of a 24-month open label, extension phase, single-centre trial. Clinical and Experimental Rheumatology. 2014;32(6 Suppl 86):S189–93.

[49] Fraticelli P, Gabrielli B, Pomponio G, et al. Low-dose oral imatinib in the treatment of systemic sclerosis interstitial lung disease unresponsive to cyclophosphamide: a phase II pilot study. Arthritis Research & Therapy. 2014;16(4);R144. doi: 10.1186/ar4606

[50] Gordon JK, Martyanov V, Magro C, et al. Nilotinib (Tasigna™) in the treatment of early diffuse systemic sclerosis: an open-label, pilot clinical trial. Arthritis Research & Therapy. 2015;17:213. doi: 10.1186/s13075-015-0721-3

[51] Postlethwaite AE, Wong WK, Clements P, et al. A multicenter, randomized, double-blind, placebo-controlled trial of oral type I collagen treatment in patients with diffuse cutaneous systemic sclerosis: I. oral type I collagen does not improve skin in all patients, but may improve skin in late-phase disease. Arthritis and Rheumatism. 2008;58(6):1810–22. doi: 10.1002/art.23501

[52] Seibold JR, Korn JH, Simms R, et al. Recombinant human relaxin in the treatment of scleroderma. a randomized, double-blind, placebo-controlled trial. Annals of Internal Medicine. 2000:132(11):871–9.

[53] Khanna D, Clements PJ, Furst DE, et al. Recombinant human relaxin in the treatment of systemic sclerosis with diffuse cutaneous involvement: a randomized, double-blind, placebo-controlled trial. Arthritis and Rheumatism;60(4):1102–11. doi: 10.1002/art.24380

[54] Distler JH, Jordan S, Airo P, et al. Is there a role for TNFα antagonists in the treatment of SSc? EUSTAR expert consensus development using the Delphi technique. Clinical and Experimental Rheumatology. 2011;29(2 Suppl 65):S40–5.

[55] Mauviel A, Daireaux M, Rédini F, et al. Tumor necrosis factor inhibits collagen and fibronectin synthesis in human dermal fibroblasts. FEBS Letters. 1988;236(1):47–52.

[56] Liu JY, Brass DM, Hoyle GW, et al. TNF-alpha receptor knockout mice are protected from the fibroproliferative effects of inhaled asbestos fibers. The American Journal of Pathology. 1998;153(6):1839–47.

[57] Piguet PF, Vesin C. Treatment by human recombinant soluble TNF receptor of pulmonary fibrosis induced by bleomycin or silica in mice. The European Respiratory Journal. 1994;7(3):515–8.

[58] Young V, Ho M, Vosper H, et al. Elevated expression of the genes encoding TNF-alpha and thromboxane synthase in leucocytes from patients with systemic sclerosis. Rheumatology (Oxford). 2002;41(8):869–75.

[59] Distler JH, Schett G, Gay S, et al. The controversial role of tumor necrosis factor alpha in fibrotic diseases. Arthritis and Rheumatism. 2008;58(8):2228–35. doi: 10.1002/art. 23645

[60] Lam GK, Hummers LK, Woods A, et al. Efficacy and safety of etanercept in the treatment of scleroderma-associated joint disease. The Journal of Rheumatology. 2007;34(7):1636–7.

[61] Denton CP, Engelhart M, Tvede N, et al. An open-label pilot study of infliximab therapy in diffuse cutaneous systemic sclerosis. Annals of the Rheumatic Diseases. 2008;68(9): 1433–9. doi: 10.1136/ard.2008.096123

[62] DrugBank: Abatacept [Internet]. Available from: http://www.drugbank.ca/drugs/ DB01281. (Accessed: 27 September 2016).

[63] NICE. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed; 2016. Available at: https:// www.nice.org.uk/guidance/TA375 (Accessed: 27 September 2016).

[64] Schiff M, Weinblatt ME, Valente R, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. Annals of the Rheumatic Diseases. 2014;73(1):86–94. doi: 10.1136/annrheumdis-2013-203843

[65] Schiff M, Keiserman M, Codding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Annals of the Rheumatic Diseases. 2007;67(8):1096–103. doi: 10.1136/ard. 2007.080002

[66] Chakravarty EF, Fiorentino D, Bennett M, et al. A pilot study of abatacept for the treatment of patients with diffuse cutaneous systemic sclerosis. Arthritis & Rheumatism. 2011;63(Suppl 10):707.

[67] Chakravarty EF, Martyanov V, Fiorentino D, et al. Gene expression changes reflect clinical response in a placebo-controlled randomized trial of abatacept in patients with diffuse cutaneous systemic sclerosis. Arthritis Research & Therapy. 2015;17:159. doi: 10.1186/s13075-015-0669-3

[68] Elhai M, Meunier M, Matucci-Cerinic M, et al. Outcomes of patients with systemic sclerosis-associated polyarthritis and myopathy treated with tocilizumab or abatacept:

a EUSTAR observational study. Annals of the Rheumatic Diseases. 2012;72(7):1217–20. doi: 10.1136/annrheumdis-2012-202657

[69] Salis P, Caccamo C, Verzaro R, et al. The role of basiliximab in the evolving renal transplantation immunosuppression protocol. Biologics: Targets & Therapy. 2008;2(2): 175–88.

[70] Thistlethwaite JR Jr, Nashan B, Hall M, et al. Reduced acute rejection and superior 1-year renal allograft survival with basiliximab in patients with diabetes mellitus. The global Simulect study group. Transplantation. 2000;70(5):784–90.

[71] Schmidt-Hieber M, Fietz T, Knauf W, et al. Efficacy of the interleukin-2 receptor antagonist basiliximab in steroid-refractory acute graft-versus-host disease. British Journal of Haematology. 2005:130(4):568–74. doi: 10.1111/j.1365-2141.2005.05631.x

[72] Becker MO, Brückner C, Scherer HU, et al. The monoclonal anti-CD25 antibody basiliximab for the treatment of progressive systemic sclerosis: an open-label study. Annals of the Rheumatic Diseases. 2010;70(7):1340–1. doi: 10.1136/ard.2010.137935

[73] Scherer HU, Burmester GR, Riemekasten G. Targeting activated T cells: successful use of anti-CD25 monoclonal antibody basiliximab in a patient with systemic sclerosis. Annals of the Rheumatic Diseases. 2006;65(9):1245–7. doi: 10.1136/ard.2005.046938

[74] Barnes TC, Anderson ME, Moots RJ. The many faces of interleukin-6: the role of IL-6 in inflammation, vasculopathy, and fibrosis in systemic sclerosis. International Journal of Rheumatology. 2011;2011:721608. doi: 10.1155/2011/721608

[75] Khan K, Xu S, Nihtyanova S, et al. Clinical and pathological significance of interleukin 6 overexpression in systemic sclerosis. Annals of the Rheumatic Diseases. 2012;71(7): 1235–42. doi: 10.1136/annrheumdis-2011-200955

[76] De Lauretis A, Sestini P, Pantelidis P, et al. Serum interleukin 6 is predictive of early functional decline and mortality in interstitial lung disease associated with systemic sclerosis. The Journal of Rheumatology. 2013;40(4):435–46. doi: 10.3899/jrheum.120725

[77] Fernandes das Neves M, Oliveira S, Amaral MC, et al. Treatment of systemic sclerosis with tocilizumab. Rheumatology (Oxford). 2015;54(2):371–2. doi: 10.1093/rheumatology/keu435

[78] Khanna D, Denton CP, Jahreis A, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. Lancet. 2016;387(10038):2630–40. doi: 10.1016/S0140-6736(16)00232-4

[79] A study of the efficacy and safety of Tocilizumab in participants with systemic sclerosis (SSc) [focuSSced] [Internet]. 2015. Available at: https://clinicaltrials.gov/ct2/show/NCT02453256 (Accessed: 27 September 2016).

[80] Hasegawa M, Hamaguchi Y, Yanaba K, et al. B-lymphocyte depletion reduces skin fibrosis and autoimmunity in the tight-skin mouse model for systemic sclerosis. The American Journal of Pathology. 2006;169(3):954–66. doi: 10.2353/ajpath.2006.060205

[81] Jordan S, Distler JH, Maurer B, et al. Effects and safety of rituximab in systemic sclerosis: an analysis from the European Scleroderma trial and research (EUSTAR) group. Annals of the Rheumatic Diseases. 2015:74(6):1188–94. doi: 10.1136/annrheumdis-2013-204522

[82] Lafyatis R, Kissin E, York M, et al. B cell depletion with rituximab in patients with diffuse cutaneous systemic sclerosis. Arthritis and Rheumatism. 2009;60(2):578–83. doi: 10.1002/art.24249

[83] Moazedi-Fuerst FC, Kielhauser SM, Brickmann K, et al. Rituximab for systemic sclerosis: arrest of pulmonary disease progression in five cases. Results of a lower dosage and shorter interval regimen. Scandinavian Journal of Rheumatology. 2014;43(3):257–8. doi: 10.3109/03009742.2013.869617

[84] Smith V, van Praet JT, Vandooren B, et al. Rituximab in diffuse cutaneous systemic sclerosis: an open-label clinical and histopathological study. Annals of the Rheumatic Diseases. 2008;69(1):193–7. doi: 10.1136/ard.2008.095463

[85] Bosello S, De Santis M, Lama G, et al. B cell depletion in diffuse progressive systemic sclerosis: safety, skin score modification and IL-6 modulation in an up to thirty-six months follow-up open-label trial. Arthritis Research & Therapy. 2010;12(2):R54. doi: 10.1186/ar2965

[86] Daoussis D, Liossis SN, Antonopoulos I, et al. THU0245 Rituximab has a beneficial effect on lung function and skin fibrosis in patients with systemic sclerosis. An open label study. Annals of the Rheumatic Diseases. 2013;71(Suppl 3):237–238. doi: 10.1136/annrheumdis-2012-eular.2210

[87] Daoussis D, Liossis SN, Tsamandas AC, et al. Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. Rheumatology (Oxford). 2010;49(2): 271–80. doi: 10.1093/rheumatology/kep093

[88] Daoussis D, Liossis SN, Tsamandas A, et al. Effect of long-term treatment with rituximab on pulmonary function and skin fibrosis in patients with diffuse systemic sclerosis. Clinical and Experimental Rheumatology. 2012;30(2 Suppl 71):S17–22.

[89] Smith V, Piette Y, van Praet JT, et al. Two-year results of an open pilot study of a 2-treatment course with rituximab in patients with early systemic sclerosis with diffuse skin involvement. The Journal of Rheumatology. 2012;40(1):52–7. doi: 10.3899/jrheum.120778

[90] Melissaropoulos K, Daoussis D, Antonopoulos I, et al. SAT0450 Rituximab in systemic sclerosis. Results of an up to seven years, open label, multicenter study with a follow-up of 89 patient-years. Annals of the Rheumatic Diseases. 2015;74(Suppl 2):823. doi: 10.1136/annrheumdis-2015-eular.4618

[91] Schiopu E, Chatterjee S, Hsu V, et al. Safety and tolerability of an anti-CD19 monoclonal antibody, MEDI-551, in subjects with systemic sclerosis: a phase I, randomized,

placebo-controlled, escalating single-dose study. Arthritis Research & Therapy. 2016;18(1):131. doi: 10.1186/s13075-016-1021-2

[92] Goldberg A, Geppert T, Schiopu E, et al. Dose-escalation of human anti-interferon-α receptor monoclonal antibody MEDI-546 in subjects with systemic sclerosis: a phase 1, multicenter, open label study. Arthritis Research & Therapy. 2014;16(1):R57. doi: 10.1186/ar4492

[93] Solans R, Bosch J, Esteban I, et al. Systemic sclerosis developing in association with the use of interferon alpha therapy for chronic viral hepatitis. Clinical and Experimental Rheumatology. 2004;22(5):625–8.

[94] Tahara H, Kojima A, Hirokawa T, et al. Systemic sclerosis after interferon alphacon-1 therapy for hepatitis C. Internal Medicine (Tokyo, Japan). 2007;46(8):473–6.

[95] Eloranta ML, Franck-Larsson K, Lövgren T, et al. Type I interferon system activation and association with disease manifestations in systemic sclerosis. Annals of the Rheumatic Diseases. 2010;69(7):1396–402. doi: 10.1136/ard.2009.121400

[96] Guo X, Higgs BW, Bay-Jensen AC, et al. Suppression of T cell activation and collagen accumulation by an Anti-IFNAR1 mAb, Anifrolumab, in adult patients with systemic sclerosis. The Journal of Investigative Dermatology. 2015;135(10):2402–9. doi: 10.1038/jid.2015.188

[97] Giordano N, Puccetti L, Papakostas P, et al. Bosentan treatment for Raynauds phenomenon and skin fibrosis in patients with systemic sclerosis and pulmonary arterial hypertension: an open-label, observational, retrospective study. International Journal of Immunopathology and Pharmacology. 2010;23(4):1185–94.

[98] Liu C, Chen J, Gao Y, et al. Endothelin receptor antagonists for pulmonary arterial hypertension. The Cochrane Database of Systematic Reviews. 2013;(2):CD004434.

[99] Launay D, Sitbon O, Le Pavec J, et al. Long-term outcome of systemic sclerosis-associated pulmonary arterial hypertension treated with bosentan as first-line monotherapy followed or not by the addition of prostanoids or sildenafil. Rheumatology (Oxford). 2010;49(3):490–500. doi: 10.1093/rheumatology/kep398

[100] Matucci-Cerinic M, Denton CP, Furst DE, et al. Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomised, double-blind, placebo-controlled trial. Annals of the Rheumatic Diseases. 2011;70(1):32–8. doi: 10.1136/ard.2010.130658

[101] Roman Ivorra JA, Simeon CP, Alegre Sancho JJ, et al. Bosentan in clinical practice for treating digital and other ischemic ulcers in Spanish patients with systemic sclerosis: IBER-DU cohort study. The Journal of Rheumatology. 2011;38(8):1631–5. doi: 10.3899/jrheum.101266

[102] Tsifetaki N, Botzoris V, Alamanos Y, et al. Bosentan for digital ulcers in patients with systemic sclerosis: a prospective 3-year followup study. The Journal of Rheumatology. 2009;36(7):1550–2. doi: 10.3899/jrheum.080992

[103] Nagai Y, Hasegawa M, Hattori T, et al. Bosentan for digital ulcers in patients with systemic sclerosis. The Journal of Dermatology. 2012;39(1):48–51. doi: 10.1111/j.1346-8138.2011.01299.x

[104] Chung L, Ball K, Yaqub A, et al. Effect of the endothelin type A-selective endothelin receptor antagonist ambrisentan on digital ulcers in patients with systemic sclerosis: results of a prospective pilot study. Journal of the American Academy of Dermatology; 71(2):400–1. doi: 10.1016/j.jaad.2014.04.028

[105] Hassoun PM, Zamanian RT, Damico R, et al. Ambrisentan and Tadalafil up-front combination therapy in scleroderma-associated pulmonary arterial hypertension. American Journal of Respiratory and Critical Care Medicine. 2015;192(9):1102–10. doi: 10.1164/rccm.201507-1398OC

[106] Saggar R, Khanna D, Shapiro S, et al. Exercise induced pulmonary hypertension in systemic sclerosis and treatment with Ambrisentan: A prospective single center, open label, pilot study. In: Proceedings of the American Thoracic Society International Conference (ATS 2011); 13–18 May 2011. doi: 10.1164/ajrccm-conference.2011.183.1_MeetingAbstracts.A5885

[107] Parisi S, Peroni CL, Laganà A, et al. Efficacy of ambrisentan in the treatment of digital ulcers in patients with systemic sclerosis: a preliminary study. Rheumatology (Oxford). 2013;52(6):1142–4. doi: 10.1093/rheumatology/ket019

[108] Hettema ME, Zhang D, Bootsma H, et al. Bosentan therapy for patients with severe Raynaud's phenomenon in systemic sclerosis. Annals of the Rheumatic Diseases. 2007;66(10):1398–9. doi: 10.1136/ard.2007.073684

[109] Shi-Wen X, Chen Y, Denton CP, et al. Endothelin-1 promotes myofibroblast induction through the ETA receptor via a rac/phosphoinositide 3-kinase/Akt-dependent pathway and is essential for the enhanced contractile phenotype of fibrotic fibroblasts. Molecular Biology of the Cell. 2004;15(6):2707–19. doi: 10.1091/mbc.E03-12-0902

[110] Shi-Wen X, Kennedy L, Renzoni EA, et al. Endothelin is a downstream mediator of profibrotic responses to transforming growth factor beta in human lung fibroblasts. Arthritis and Rheumatism. 2007;56(12):4189–94. doi: 10.1002/art.23134

[111] Reichenberger F, Schauer J, Kellner K, et al. Different expression of endothelin in the bronchoalveolar lavage in patients with pulmonary diseases. Lung. 2002;179(3):163–74. doi: 10.1007/s004080000058

[112] Seibold JR, Denton C, Furst DE, et al. Randomized, prospective, placebo-controlled trial of bosentan in interstitial lung disease secondary to systemic sclerosis. Arthritis and Rheumatism. 2010;62(7):2101–8. doi: 10.1002/art.27466

[113] Furuya Y, Kuwana M. Effect of Bosentan on systemic sclerosis-associated interstitial lung disease ineligible for cyclophosphamide therapy: a prospective open-label study. The Journal of Rheumatology. 2011;38(10):2186–92. doi: 10.3899/jrheum.110499

[114] Kuhn A, Haust M, Ruland V, et al. Effect of bosentan on skin fibrosis in patients with systemic sclerosis: a prospective, open-label, non-comparative trial. Rheumatology (Oxford). 2010;49(7):1336–45. doi: 10.1093/rheumatology/keq077

[115] Khanna D, Denton CP, Merkel PA, et al. Effect of Macitentan on the development of new ischemic digital ulcers in patients with systemic sclerosis: DUAL-1 and DUAL-2 Randomized clinical trials. JAMA. 2016;315(18):1975–88. doi: 10.1001/jama.2016.5258

[116] Fava A, Wung PK, Wigley FM, et al. Efficacy of Rho kinase inhibitor fasudil in secondary Raynaud's phenomenon. Arthritis Care & Research (Hoboken). 2012;64(6):925–9. doi: 10.1002/acr.21622

[117] Herrick AL, Murray AK, Ruck A, et al. A double-blind, randomized, placebo-controlled crossover trial of the α2C-adrenoceptor antagonist ORM-12741 for prevention of cold-induced vasospasm in patients with systemic sclerosis. Rheumatology (Oxford). 2014;53(5):948–52. doi: 10.1093/rheumatology/ket421

[118] Zibotentan better renal Scleroderma outcome study - full text view [Internet]. 2014. Available at: https://clinicaltrials.gov/show/NCT02047708 (Accessed: 27 September 2016).

[119] A study of Subcutaneous Abatacept to treat diffuse cutaneous systemic sclerosis [Internet]. 2014. Available at: https://clinicaltrials.gov/ct2/show/NCT02161406 (Accessed: 27 September 2016).

[120] Proof-of-concept trial of IVA337 in diffuse cutaneous systemic sclerosis [Internet]. 2015. Available at: https://clinicaltrials.gov/show/NCT02503644 (Accessed: 27 September 2016).

[121] Ruzehaji N, Frantz C, Ponsoye M, et al. Pan PPAR agonist IVA337 is effective in prevention and treatment of experimental skin fibrosis. Annals of the Rheumatic Diseases. 2016. doi: 10.1136/annrheumdis-2015-208029

[122] A trial to compare Nintedanib with placebo for patients with scleroderma related lung fibrosis [Internet]. 2015. Available at: https://clinicaltrials.gov/show/NCT02597933 (Accessed: 27 September 2016).

[123] Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. The New England Journal of Medicine. 2014;370(22):2071–82. doi: 10.1056/NEJMoa1402584

[124] Huang J, Beyer C, Palumbo-Zerr K, et al. Nintedanib inhibits fibroblast activation and ameliorates fibrosis in preclinical models of systemic sclerosis. Annals of the Rheumatic Diseases. 2016;75(5):883–90. doi: 10.1136/annrheumdis-2014-207109

[125] Efficacy and safety of Riociguat in patients with systemic sclerosis [Internet]. 2014 Available at: https://clinicaltrials.gov/show/NCT02283762 (Accessed: 27 September 2016).

[126] Prey S, Ezzedine K, Doussau A, et al. Imatinib mesylate in scleroderma-associated diffuse skin fibrosis: a phase II multicentre randomized double-blinded controlled trial. The British Journal of Dermatology. 2012;167(5):1138–44. doi: 10.1111/j. 1365-2133.2012.11186.x

[127] Guo L, Chen XX, Gu YY, et al. Low-dose imatinib in the treatment of severe systemic sclerosis: a case series of six Chinese patients and literature review. Clinical Rheumatology. 2012;31(9):1395–400. doi: 10.1007/s10067-012-2032-2

[128] Tamaki Z, Asano Y, Hatano M, et al. Efficacy of low-dose imatinib mesylate for cutaneous involvement in systemic sclerosis: a preliminary report of three cases. Modern rheumatology/the Japan Rheumatism Association. 2011;22(1):94–9. doi: 10.1007/s10165-011-0472-1

[129] Sabnani I, Zucker MJ, Rosenstein ED, et al. A novel therapeutic approach to the treatment of scleroderma-associated pulmonary complications: safety and efficacy of combination therapy with imatinib and cyclophosphamide. Rheumatology (Oxford). 2008;48(1):49–52. doi: 10.1093/rheumatology/ken369

[130] De Paoli FV, Nielsen BD, Rasmussen F, et al. Abatacept induces clinical improvement in patients with severe systemic sclerosis. Scandinavian Journal of Rheumatology. 2014;43(4):342–5. doi: 10.3109/03009742.2013.812238

[131] Cutolo M, Ruaro B, Pizzorni C, et al. Longterm treatment with endothelin receptor antagonist bosentan and iloprost improves fingertip blood perfusion in systemic sclerosis. The Journal of Rheumatology. 2014;41(5):881–6. doi: 10.3899/jrheum.131284

[132] Romaniello A, Viola G, Salsano F, et al. In systemic sclerosis patients, bosentan is safe and effective for digital ulcer prevention and it seems to attenuate the development of pulmonary arterial hypertension. Rheumatology (Oxford). 2013;53(3):570–1. doi: 10.1093/rheumatology/ket424

[133] Taniguchi T, Asano Y, Hatano M, et al. Effects of bosentan on nondigital ulcers in patients with systemic sclerosis. The British Journal of Dermatology. 2011;166(2):417–21. doi: 10.1111/j.1365-2133.2011.10581.x

[134] Rosato E, Molinaro I, Borghese F, et al. Bosentan improves skin perfusion of hands in patients with systemic sclerosis with pulmonary arterial hypertension. The Journal of Rheumatology. 2010;37(12):2531–9. doi: 10.3899/jrheum.100358

[135] Nguyen VA, Eisendle K, Gruber I, et al. Effect of the dual endothelin receptor antagonist bosentan on Raynaud's phenomenon secondary to systemic sclerosis: a double-blind prospective, randomized, placebo-controlled pilot study. Rheumatology (Oxford). 2009;49(3):583–7. doi: 10.1093/rheumatology/kep413

[136] Funauchi M, Kishimoto K, Shimazu H, et al. Effects of bosentan on the skin lesions: an observational study from a single center in Japan. Rheumatology International. 2008;29(7):769–75. doi: 10.1007/s00296-008-0789-z

[137] Denton CP, Pope JE, Peter HH, et al. Long-term effects of bosentan on quality of life, survival, safety and tolerability in pulmonary arterial hypertension related to connective tissue diseases. Annals of the Rheumatic Diseases. 2007;67(9):1222–8. doi: 10.1136/ard.2007.079921

[138] García de la Peña-Lefebvre P, Rodríguez Rubio S, Valero Expósito M, et al. Long-term experience of bosentan for treating ulcers and healed ulcers in systemic sclerosis patients. Rheumatology (Oxford). 2008;47(4):464–6. doi: 10.1093/rheumatology/ken001

[139] Sfikakis PP, Papamichael C, Stamatelopoulos KS, et al. Improvement of vascular endothelial function using the oral endothelin receptor antagonist bosentan in patients with systemic sclerosis. Arthritis and Rheumatism. 2007;56(6):1985–93. doi: 10.1002/art.22634

[140] Moore TL, Vail A, Herrick AL. Assessment of digital vascular structure and function in response to bosentan in patients with systemic sclerosis-related Raynaud's phenomenon. Rheumatology (Oxford). 2006;46(2):363–4. doi: 10.1093/rheumatology/kel383

[141] Selenko-Gebauer N, Duschek N, Minimair G, et al. Successful treatment of patients with severe secondary Raynaud's phenomenon with the endothelin receptor antagonist bosentan. Rheumatology (Oxford). 2006;45(Suppl 3):iii45–8. doi: 10.1093/rheumatology/kel290

[142] Ahmadi-Simab K, Hellmich B, Gross WL. Bosentan for severe pulmonary arterial hypertension related to systemic sclerosis with interstitial lung disease. European Journal of Clinical Investigation. 2006;36(Suppl 3):44–8. doi: 10.1111/j.1365-2362.2006.01695.x

[143] Meijs J, Voskuyl AE, Bloemsaat-Minekus JP, et al. Blood flow in the hands of a predefined homogeneous systemic sclerosis population: the presence of digital ulcers and the improvement with bosentan. Rheumatology (Oxford). 2015;54(2):262–9. doi: 10.1093/rheumatology/keu300

[144] Denton CP, Humbert M, Rubin L, et al. Bosentan treatment for pulmonary arterial hypertension related to connective tissue disease: a subgroup analysis of the pivotal clinical trials and their open-label extensions. Annals of the Rheumatic Diseases. 2006;65(10):1336–40. doi: 10.1136/ard.2005.048967

[145] Chung L, Ball K, Yaqub A, et al. Effect of the endothelin type a-selective endothelin receptor antagonist ambrisentan on digital ulcers in patients with systemic sclerosis: results of a prospective pilot study. Journal of the American Academy of Dermatology. 2014;71(2):400–1. doi: 10.1016/j.jaad.2014.04.028

[146] Bose N, Bena J, Chatterjee S. Evaluation of the effect of ambrisentan on digital microvascular flow in patients with systemic sclerosis using laser Doppler perfusion imaging: a 12-week randomized double-blind placebo controlled trial. Arthritis Research & Therapy. 2015;17:44. doi: 10.1186/s13075-015-0558-9