Systemic sclerosis: from pathogenesis to targeted therapy

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ABSTRACT

Systemic sclerosis (scleroderma) leads to morbidity and mortality through a combination of inflammation, fibrosis and vascular damage leading to internal organ complications affecting the heart, lung, kidneys and bowel. More than half of those diagnosed ultimately die from the disease. Current treatments focus on broad spectrum immunosuppression or organ-based therapy for complication such as lung fibrosis, pulmonary or systemic hypertension. Targeting peptide mediators such as endothelin-1 have already led to licensed effective therapies for SSc vasculopathy. Outcomes are improving but as well as providing a major clinical challenge there are great opportunities for research translation that can be expected to improve understanding of the pathogenesis of SSc and also develop better and more targeted therapy. Key pathways and mediators can be identified within the skin and blood vessels and these are now being examined in early stage clinical trials. Promising results are emerging from targeting cytokine signalling, including IL-6, and from other immune-inflammatory therapies including lipid mediators such as LPA1. Other approaches to modulate TGFbeta and other profibrotic pathways also have potential although safety and toxicity remain to be determined. Since many profibrotic pathways have important physiological roles the assessment of safety and toxicity will be paramount. Nevertheless, advances in understanding the interplay between different pathological processes and progress in clinical trial design and patients stratification mean that targeted therapies are emerging and likely to be further developed and refined to have application in other important clinical contexts such as lung fibrosis.

Systemic sclerosis is the autoimmune rheumatic disease with the highest case specific mortality with more than half of cases dying as a direct result of the disease, mostly from cardiorespiratory complications. The internal organ manifestations occur in both of the major subsets of the disease that are determined by the extent of skin involvement. Diffuse SSc cases have skin thickening involving the proximal limbs or trunk and these cases have a higher frequency of heart, lung or kidney involvement especially in the first 3 years from disease onset. There have been substantial advances in the management of systemic sclerosis that have led to better overall survival, especially for the most severe diffuse form of the disease. These have included better management of specific organ based complications as well as more systematic follow up and investigation of cases. This proactive approach allows complications to be identified sooner and may permit earlier or more effective therapy (1). In addition there have been advances in understanding of pathogenesis. This remains incomplete understood but has reached a point where key cell types and potential mediators can be defined, this makes the concept of targeted therapy more real and has started to inform clinical development and trials (2). Several strategies have been developed and some have already been explored in clinical trials. In addition there have been three recent placebo controlled trials that offer hope in that there have been differentiation of placebo and active treatment response (3). This builds upon the platform of data emerging to support the value of immunosuppression in various aspects of the disease, especially skin and lung fibrosis. This is most clearly shown by encouraging results from stem cell transplant studies that point to improved long term survival and functional outcome albeit at the cost of potentially important treatment related mortality in up to 10% of cases (4). Some complications such as pulmonary hypertension occur with equal frequen-

cy in both of the major disease subsets and may occur later in the disease (5). Not all manifestations are life threatening, but complications sunk as digital ulceration, anorectal disease and secondary Raynaud's together with musculoskeletal involvement are important though their impact on quality of life. Constitutionals features such as severe fatigue, pain and psychosocial impact are also major consequences and these are often poorly addressed (6).

The concept of targeted therapy for SSc can have several different meanings. First is the consideration of targeting specific organ based complications such as scleroderma renal crisis. Pulmonary arterial hypertension or lung fibrosis or specific symptoms such as Raynaud's phenomenon or gastro-oesophageal reflux (7). Another view of targeted therapy is the treatment of individual disease processes such as immune activation, inflammation, vascular disease or fibrosis. Finally there may be opportunities to tackle specific cell types or cellular interactions that may target several aspects of the disease through the same mechanism. The most specific connotation for targeted therapy is the attenuation or stimulation of a specific intracellular target or pathway that may then impact on multiple processes within disease pathogenesis. However, as in other areas of medicine the term is rather over-used and much be precisely defined to be useful. In essence it is difficult to define any therapy as not targeted and so the concept is often synonymous with new or novel approaches to the disease and especially to biological agents. In this context there recent clinical trials that have differentiated active treatment rom placebo may be described as targeted therapy in SSc (8).

Treatment of skin and lung fibrosis in SSc forms the mainstay of current clinical practice and some of the agents that are in current use include drugs that are used in treatment of other autoimmune rheumatic diseases. Many are broad spectrum immunosuppressive strategies and this emphasises the importance inflammation in the disease, familiarity with these approaches and th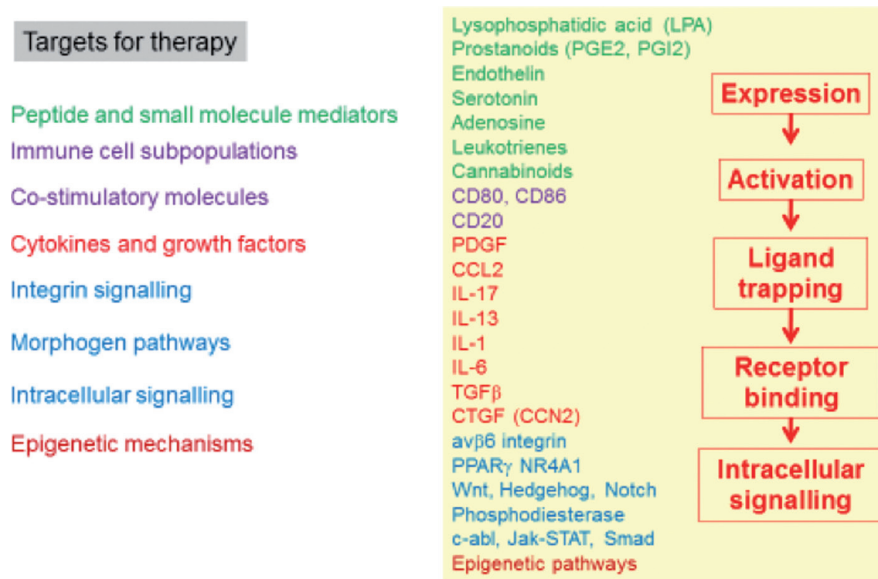e particular challenge of trying to tackle the fab-ric or scarring aspects of the condition. Thus agents in use include methotrexate, cyclophosphamide, azathioprine, Mycophenolate mofetil and autologous stem cell transplantation (9). There is an emerging evidence base supporting each of these approaches that is beyond the scope of this article. However it is generally accepted that the effectiveness of these treatments is limited, other than for stem cell transpirations where long term benefit is implied in controlled trials but at a potential cost of high treatment related mortality. This reflects the inherent challenge of giving high intensity chemotherapy to patients with severe SSc that may have severe lung and kidney involvement that makes immunosuppression, high fluid loads, sepsis and the direct toxicity of chemotherapeutic agents especially challenging. Recent clinical trials of more targeted treatments have focused on skin disease and all have targeted inflammatory to immunological mechanisms primarily.

Although SSc is an autoimmune disease and inflammation in the skin is an important feature in the early stages of the condition, especially in the diffuse subset, there are clearly other aspects to the pathogenesis. Thus although most patients have one of the hallmark autoantibodies including ACA, ATA or ARA, the main pathology of the disease in skin and internal organs has more similarity to tissue repair and would healing (10). Thus the biology of excisional wound healing peonies a realistic paradigm for the changes that occur in SSc as fibrosis develops. All of the cell types relevant to the disease pathogenesis are likely to be present in excisional skin wound harling with the generation of a fibrogenic population of alphaSMA rich myofibroblasts and these generate scar tissue appropriated. However in normal would healing these myofibroblasts undergo apoptosis and then allowed appropriate resolution. This switch off process may be the key abnormality in fibrosis in the skin and elsewhere had is less well understood than the initiating factors in inflammation or tissue injury response (11).

Preclinical mouse models offer a valu-able insight into pathogenies mechanism and aloe hypothesis of pathogenesis to be tested *in vivo*. In add-on, when they accurately reflect the pathology of the disease these models also provide a platform for experimental therapeutics. There are several mdels curerntlky avaialabkle inclduging gene targeted genetic models, spontaneous mutant strains and chemically induced models of fibrosis in the skin and lung. One model that has been well characterised over recent years involves the genetic activation of TGFbeta signalling pathways in fibroblast and leads to organ based fibrosis with ligand dependent activation of TGFbeta signalling in skin and internal organs. This mouse strains develops skin fibrosis as well and changes in the gut and heart that are reminiscent of SSc (12, 13, 14). In addition other lung complications of SSc may be induced by injury of the epithelial compartments and also mist recently by induction of endothelial ell injury using VEGFR2 inhibition. This leads to the development of a pulmonary hypertension phenotype that can be attenuated by agents that block the endothelin axis such as macitentan, this model Shas also provided insight into the development of PAH by demo staring down regulation of BMP signalling in part due to reduced levels of BMPRII. It appears that TGFbeta activation reduced the surface expression of BMPRII via a mechanisms that involved increased proteasome degradation. This has provided key insight into the development of PAH in SSc (15).

Thus, it is clear that there is now a much better understanding of the potential interplay between the innate and adaptive immune system and the vascular disease of SSc in the microcirculations an the larger vessels as well as an appreciation that these events are functionally linked to the development of inappropriate fibrotic response. Thus SSc can be seen as a phenotype of dysregulated tissue repair that occurs in a variety of organs and systems. It is plausible to consider how the key pathways that are likely to underpin this development of fibrosis can be defined and then the mediators that are central to the pathway, this provides a list of

Targets for therapy

Peptide and small molecule mediators
Immune cell subpopulations
Co-stimulatory molecules
Cytokines and growth factors
Integrin signalling
Morphogen pathways
Intracellular signalling
Epigenetic mechanisms

Lysophosphatidic acid (LPA)
Prostanoids (PGE2, PGI2)
Endothelin
Serotonin
Adenosine
Leukotrienes
Cannabinoids
CD80, CD86
CD20
PDGF
CCL2
IL-17
IL-13
IL-1
IL-6
TGFβ
CTGF (CCN2)
avβ6 integrin
PPARγ NR4A1
Wnt, Hedgehog, Notch
Phosphodiesterase
c-abl, Jak-STAT, Smad
Epigenetic pathways

Expression → Activation → Ligand trapping → Receptor binding → Intracellular signalling

Fig. 1. Targeting mechanisms of connective tissue repair vasculopathy and fibrosis.
Interplay between the vascular, immune and connective tissue compartments is likely to be central to the pathogenesis of systemic sclerosis and pathways or processes that are relevant can be inferred from growing understanding of disease neology. Within these pathways key mediators may be targeted or signalling pathways attenuated in ways that may benefit the disease, drawing analogy with other strategies that have been effective of treating autoimmune rheumatic disease.

Table I. Potential therapeutic strategies for blocking TGFbeta.

• CAT-192 ineffective but safe
  – Denton *et al*. Arthritis Rheum 2007, 56:323-33
    • Mono-specific for TGFb1
    • Weak ligand binding *in vitro*

• Pan-specific agents currently in development
  – Fresolimumab (GC1008) effectively blocks all isoforms of TGFb
    • phase I study in dcSSc underway with promising molecular data and safety profile (Lafyatis *et al*., JCI, 2015)
  – Recombinant soluble TbRII fusion protein
  – ALK5 inhibitors likely to be limited by toxicity
  – Betaglycan derived TGFb binding peptide
    • under evaluation topically

• Downstream pathways/mediators are being targeted
  – cAbl (imatinib), CTGF, Smad7, NR4A1

• Cross-modulating pathways are targeted
  – ETRA, CCR antagonists, others

candidate targets for therapy and some are already amenable to therapeutic modulation. In essence this provides a roadmap for clinical, trails of therapies that may also inform about the likely key mediators of a pathogenesis. The potential pathways and mediators that might emerge as feasible and effective in SSc are indicated in Figure 1.
Of these pathways TGFbeta signalling is a particularly attractive candidate, based on the preclincila data outlined above. There have now been two clinical trials of antibodies that block TGF-beta, the first of these used a weak monospecific antibody. This blocked only TGFbeta and did not shoe clinical benefit in a small clinical trial of skin dieses. However there were also no safety concerns (16). This is important when the pleotropic effects of TGFbeta on multiple cell types is considered. Very recently another clinical trials has been described that blocks TGFbeta more effectively and although this was an open label study it does suggest that the skin score may be improved and that gene expression signatures may be attenuated with their treatment (17). The durability and clinical meaning of this remains to be determent in future studies but this recently published clinical trial provides strong support top the rationale for targeting TGFbeta in SSc especially for skin disease. Other approaches to TGFbeta blockade are possible and are summarised in Table I. Another novel approach that has some promise is the use of hyperimmune caprine serum. This preparation is administered after rapid thawing twice a week by subcutaneous injection and is known to include a number of putative biological molecules that may target inflammation or fibrosis but has been shown to improve skin sclerosis in a study of late stage dcSSc (18). The molecular basis of this clinical response is currently under evaluation. Targeting lipid mediator pathways such as lysophosphatidic acid have also been used and shone promise in a biomarker driven clinical trials (19, 20, 21).
Possibly the most immediate clinical potential comes from trials that have examined the effect of agents that are already licensed for other indications. Thus, blockade of IL6 activity seems to be beneficial for SSc skin disease and has shoe suggested benefit in prevention of regression of lung disease. Thus a clinical trial is now completed and another about to start using tocilizumab, an IL6R blocker that is license for treatment of RA bad some other rare diseases. This is based upon the rationale that cases of SSc with increased IL6 activity have worse outcome and refractory skin do ease with increased mortality (22, 23).
In conclusion, there is real potential for targeted therapy that modulates key mediators or pathways in SSc and this is now emerging as a theme for clinical trials. Some approaches are summarised in Table II. These have focused on skin or disease but provide a strong direction of travel for the immediate future. It might be concluded that concepts of pathogenesis have progressed to the extent that logical targets and therapeutics can be teased based on studies of desease tissue and preclinical models and that this may allow progress. Studies that define expression

Table II. Candidate molecular therapies for different aspects of systemic sclerosis.

Candidate therapy	Target pathway
VASCULAR	
• Bosentan, macitentan	ET_A/ET_B receptor
• Ambrisentan	ET_A receptor
• Selexipag	IP receptor agonist
• Riociguat	cGMP agonist
INFLAMMATION	
• Infliximab, Adalimumab	TNF-α ligand
• Etanercept	TN-α ligand
• Rituximab	CD20
• Basiliximab	IL-2Rα
• MLM-1202	CCR2
• Efalizumab	LFA1/ICAM-1
• Abatacept	CTLA4
• AIMSPRO® (HCS)	αMSH, IL10, CCL2
• Tocilizumab	IL-6R
• ACT12339	LPA_1
FIBROSIS	
• Imatinib, Dasatinib, Nilotinib	c-Abl, c-Kit, PDGF
• CAT-192	TGFβ1
• GC-1008	TGFβ1,-β2,-β3
• FG-3019	CCN2
• P144	TGFβ1 (topical)
• Anti-αvβ6 integrin	TGFβ activation
• Pirfenidone	TNFα, IL1β, TGFβ
• Nintedanib (BIBF1120)	VEGF,PDGF,FGF

of targets are likely to underpin future strategies for treatment. Clinical trials provide the best way of testing these hypothesis and are also likely to underpin clinical regress. It is now more likely than not that effective targeted approaches for certain subgroups of SSc or specific complications will be developed over the next few years and new challenges are emerging such as case selection, cohort enrichment and completion between clinical trials. This includes the repurposing of agents licensed for other indications that have underlined the potential for disease modification in other complex diseases such as vasculitis and arthritis (25). SSc remains ad very serious illness but is poised to have more progress and nihilism is no longer appropriate in terms soft therapeutics fort this disease. Parallel studies in biology of fibrosis are suggesting new potential targets (26) and this means that the future possibilities for antifibrotic therapy are increasing and have potential beyond SSc in other commoner forms of organ-based fibrosis.

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