

Systemic sclerosis phase III clinical trials – hope on the horizon?

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Abstract

While significant progress has been made in treating systemic sclerosis, many patients still have an outcome that is far from satisfactory. For the first time in history, several drugs are now in phase III randomized controlled trials. Approaches tested include the anti-B cell antibody rituximab, the anti-interleukin-6 receptor antibody tocilizumab, the antifibrotic drugs nintedanib and pirfenidone and the cannabinoid receptor mimetic lenabasum. That all these drugs are in advanced clinical trials despite the relatively low incidence of the disease therefore is good news. Not only is there realistic hope that at least some of the approaches will work, this also indicates growing industry interest, for most of the trials are company-sponsored. This review attempts to delineate the ongoing trials and to summarize the underlying evidence of these candidate systemic sclerosis drugs.

Key words: scleroderma, therapy, inflammatory, fibrotic, B cells, cytokines

Systemic sclerosis (SSc) is arguably the most difficult to treat autoimmune rheumatic disease today. The number of drugs that are definitively helpful in treating SSc is small (1), and none of the therapeutic approaches is sufficiently safe and beneficial as of today (2), and when leaving aside pulmonary arterial hypertension, in particular.

When we look at the actual evidence from phase III trials, we have two commercial studies that showed bosentan helpful in the prophylaxis, but not healing, of SSc digital ulcers (3;4). We have the two Scleroderma Lung Study trials, which proved (limited) efficacy of cyclophosphamide in SSc interstitial lung disease (ILD)(5) and a similar effect of mycophenolate mofetil (MMF), respectively (6). We now have two trials showing autologous stem cell transplantation superior to cyclophosphamide, albeit at the price of significant procedure-associated early mortality (2;7). Finally, although not from randomized controlled trials (RCTs), we have convincing evidence for a role of angiotensin converting enzyme (ACE) inhibitors in SSc renal crisis (1). All of these trials have tremendous importance. Nevertheless, the options we can now offer our patients are partly sufficient at best.

Several reasons may together explain this lack of fully adequate therapies. In part, this is still due to insufficient understanding of SSc pathophysiology. While we understand today that SSc involves both endothelial damage and tissue fibrosis, and while we are also able to more precisely subgroup patients based on autoantibodies (8-10), the underlying mechanisms of disease are still rather hypothetical. Nevertheless, some of the insights have led to clinically testable hypotheses. Another part of the problem is the relatively low incidence of SSc, which has made larger clinical trials very difficult, which has in part been overcome by combining forces, mainly through EUSTAR, the EULAR scleroderma trials and research group (11). Also related to the low incidence is the historically limited interest of pharmaceutical companies in the disease. This issue has been partly resolved by legislation favoring orphan drugs. Accordingly, the number of advanced clinical trials is slowly increasing, and it appears worthwhile to look at the ongoing phase III trials. This manuscript attempts to point out these trials and provide background on the approaches taken.

Methods

Clinicaltrials.gov was queried for phase III controlled trials in patients with systemic sclerosis (last on February 1, 2018). These advanced clinical trials included three on biological DMARDs, namely on tocilizumab and rituximab, and three on oral drugs, namely on lenabasum, nintedanib and pirfenidone (Table 1). For each of these drugs, the published literature regarding use in systemic sclerosis or related fields was reviewed. Results were ordered by NCT numbers

Table 1: Ongoing controlled phase III clinical trials in systemic sclerosis

Rituximab

NCT01248084 RECOVER Sponsor: Assistance Publique – Hôpitaux des Paris

1 g rituximab day 1 and 15 vs. placebo

Duration 6 (12) months

Inclusion: SSc with polyarthritis (≥ 4 swollen joints)

Primary endpoint: Number of tender and swollen joints

Secondary endpoints include:

- SSc-HAQ
- mRSS
- FVC

NCT01862926 RECITAL Sponsor: Royal Brompton & Harefield NHS Foundation Trust

1g rituximab day 1 and 15 vs cyclophosphamide 600 mg/m² q 4 weeks for 6x

Duration 48 weeks

Inclusion: SSc or PM/DM or MCTD with ILD

Primary endpoint: Absolute change in FVC

Secondary endpoints include:

- Change in DLCO
- Change in HR-QoL
- Progression free survival

Tocilizumab

NCT02453256 focuSSced Sponsor: Hoffmann-La Roche

162 mg tocilizumab q week vs. placebo

Duration 48 weeks, open label extension trial

Inclusion: SSc with mRSS 10-35

Primary endpoint: Change in mRSS from week 0 to week 48

Secondary endpoints include:

- Proportion 20/40/60% mRSS improvement
- Change in FVC
- Change in HAQ-DI
- Digital ulcers

Nintedanib

NCT02597933 SENSICIS Sponsor: Boehringer Ingelheim

Nintedanib 150 mg bid vs. placebo

Duration 52 weeks, open label extension trial (NCT03313180)

Inclusion: SSc with ILD ($\geq 10\%$ on CT)

Primary endpoint: Annual rate of decline in FVC (ml)

Secondary endpoints include:

- Time to all-cause-mortality
- Change in mRSS
- Change in SHAQ
- Digital ulcers

Pirfenidone

NCT03068234 Sponsor: RenJi Hospital

Pirfenidone 200 mg tid vs. placebo

Duration: 24 weeks

Inclusion: SSc with mRSS ≥ 10

Primary endpoint: mRSS

Secondary endpoints include:

- Chest CT
- FVC
- QoL

Lenabasum

NCT03398837 RESOLVE-1 Sponsor: Corbus Pharmaceuticals Inc.

Lenabasum 5 mg or 20 mg bid vs. placebo

Duration 1 year

Inclusion: dcSSc

Primary endpoint: Change in mRSS

Secondary endpoints include:

- Change in HAQ-DI
- ACR combined response index (ACR CRISS)
- Change in FVC

Rituximab

Rituximab is a chimeric monoclonal antibody against CD20, a protein exclusively present on the surface of B cells, but not on early B cell precursors or plasma cells (12). Rituximab depletes B cells almost completely, but does not usually diminish immunoglobulin severely (13). Rituximab was first approved for B cell malignancies, but is also approved for treating rheumatoid arthritis (14) and ANCA associated vasculitides (15;16). Rituximab is marketed by Roche. The drug is out of patent and biosimilars have been approved.

There are currently two ongoing rituximab trials in systemic sclerosis, locally sponsored in France and the UK, respectively. Both trials use 1 g rituximab at day 1 and 15, as in rheumatoid arthritis. The French trial RECOVER (NCT01248084) focusses on joint disease, and accordingly has the swollen and tender joint count as its primary endpoint, but also looks at forced vital capacity (FVC) and modified Rodnan's skin score (mRSS). The UK trial RECITAL (NCT01862926) has a focus on interstitial lung disease, in contrast, and also includes patients with other connective tissue diseases (CTDs), namely mixed connective tissue disease (MCTD) and inflammatory myopathies (poly- and dermatomyositis) (17). Its primary endpoint is the absolute change in FVC.

Both trials are based on sound hypotheses. Rituximab is approved for rheumatoid arthritis, but there are also observational data that it may be effective in the arthritides of CTDs (18). Likewise, there is a significant body of observational data indicating rituximab efficacy for interstitial lung disease in CTDs (19-22). Despite changes in SSc autoantibodies following rituximab (23), the main mechanism

apparently is not downmodulation of autoantibodies. Instead, the removal of cytokine producing B cells, with reduced IL-6 shown after rituximab in SSc (24), but particularly the loss of specific antigen presentation by B cells are discussed as the main mechanisms of action. B cells are indeed present in SSc skin, and get depleted by rituximab (25), which also reduced myofibroblasts and hyalinized collagen (25), as well as fibroblast type I collagen production (26).

While there are no controlled trial data so far, rituximab use in SSc is apparently widespread, with 63 SSc patients included into a 2015 EUSTAR paper (22). This paper found indications of improved skin thickening, with MRSS falling from 27 ± 1 to 20 ± 2 in 25 rituximab-treated SSc patients, but not matched controls, and stabilization of interstitial lung disease in 9 rituximab-treated patients (with concomitant fall in the matched controls). Smaller case series also suggest positive effects on the MRSS (21;24;27-29), and an increase in FVC (21;27;30) and DLCO (21;30).

Tocilizumab

Tocilizumab is a humanized monoclonal antibody against the human interleukin-6 (IL-6) receptor α chain (31). Tocilizumab blocks IL-6 signalling almost completely, and is approved for treating rheumatoid arthritis (32), systemic onset juvenile idiopathic arthritis (33) and giant cell arteritis (34). Tocilizumab is co-marketed by Roche and Chugai.

The ongoing phase III clinical trial focuSSced (NCT02453256) sponsored by Roche is placebo-controlled and included patients with early diffuse cutaneous SSc (dcSSc). FocuSSced has an improvement in modified Rodnan's Skin Score (mRSS) as its primary endpoint (Table 1). Key secondary endpoints include lung function tests and patient related outcome parameters.

The original idea stems from several ex vivo findings (35), and data that high amounts of IL-6 in SSc sera contain correlate with mRSS (36), in particular. In addition, higher levels of IL6 appeared to reflect poor prognosis from lung fibrosis in SSc and higher mortality (37) with more persistently severe skin sclerosis (38). Early case reports suggest rapid skin score improvement (39). The consequence was faSScinate, a phase II clinical trial. FaSScinate randomized 87 patients with dcSSc of not more than 5 years disease duration 1:1 (43:44) to a weekly 162 mg s.c. injection of tocilizumab or a placebo injection over 48 weeks (40). The primary endpoint was the mean change in mRSS from baseline to 24 weeks. While missing the primary endpoint, there was a trend towards greater improvement in mRSS at 24 weeks (-3.92 vs. -1.22, $p=0.0915$), which approached significance at 48 weeks (-6.33 vs. -2.77, $p=0.0579$). Tocilizumab treated patients had a trend towards more commonly reaching 20% mRSS improvement at week 24 (37% vs. 27%, $p=0.36$), and were significantly more likely to reach a 60% mRSS decrease (12% vs 0%, $p=0.026$) or a clinically important improvement of ≥ 4.7 units (37% vs

25%, $p=0.025$) by week 48. Importantly, forced vital capacity (FVC) was significantly less decreased after 24 weeks of tocilizumab than under placebo (-34 mL vs. -171 mL, $p=0.0368$).

With the consecutive open-label period, 63% of the tocilizumab-treated and 55% of the placebo-treated patients completed 96 weeks (41). The patients of the tocilizumab group improved further in mRSS to -9.3 at 72 weeks and stabilized at -9.1 at 96 weeks. The patients switched from placebo to open label tocilizumab had an improvement of -5.2 units at 72 weeks and reached -9.4, the same level of improvement as the original tocilizumab group, at week 96, after one year of tocilizumab therapy. Of the 30 patients in the tocilizumab group who finished 96 weeks, 22 (73%) had ≥ 4.7 mRSS units improvement, as had 19 of the 24 (79%) of the group switched from placebo to tocilizumab. In the open-label period no patient had a $>10\%$ decline in FVC, as compared to 3 in the placebo group and 1 in the tocilizumab group during the placebo-controlled phase.

In total, four patients died in the placebo-controlled phase, 3 of whom were in the tocilizumab arm. However, only one of the deaths, due to pneumonia, was considered possibly treatment related. No patient died during the open label extension phase.

Nintedanib

Nintedanib is a relatively non-selective tyrosine kinase inhibitor, which inhibits the kinase activity of various growth factor receptors, including those of vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF)(42). Nintedanib is approved for treatment of idiopathic pulmonary fibrosis (IPF)(43), and is also being tested for several malignancies. Nintedanib is owned and marketed by Boehringer Ingelheim.

SENSCIS (NCT02597933), the ongoing phase III clinical trial in SSc-related lung fibrosis (44) sponsored by Boehringer Ingelheim is placebo controlled and includes patients with dcSSc, at least 10% lung fibrosis on chest CT and $FVC \geq 40\%$ of the predicted value. The primary endpoint is mL decline in FVC assessed at 52 weeks (Table 1). Secondary endpoints include other measures of lung function, time to all cause mortality, SSc digital ulcers and mRSS. Cases are stratified according to the use of concurrent immunosuppression with mycophenolate mofetil or methotrexate. These agents are used as standard background therapy for systemic sclerosis in many centres, as evidenced by the recently reported European Scleroderma Observational Study (ESOS) that demonstrated improvement in skin score with both drugs after statistical adjustment for potential baseline confounding factors (45). In SENSCIS these agents should be at stable dose at the time of randomization to nintedanib or placebo.

The original hypothesis is based on similarities in lung fibrosis between IPF and SSc-interstitial lung disease. In IPF, where no treatment option other than lung transplantation had previously existed, nintedanib has been proven to not only reduce the decline in FVC, but to also actually improve survival

(43). The IPF trials had in part been based on animal data using the bleomycin model of fibrosis (46), which is also regarded relevant to SSc pathophysiology, at least to some degree. Recently, nintedanib was also shown to ameliorate both fibrotic and vascular manifestations of Fra2-transgenic animals (47), which have manifestations rather similar to patients with dcSSc.

Since there are no SSc data available yet, we can only look at the two replicate phase III IPF studies INPULSIS-1 and 2 (48) instead. In these trials, 1,066 IPF patients were, in a 3:2 ratio, randomized to 150 mg nintedanib b.i.d. or placebo. Reduction in FVC was significantly lower in the nintedanib than in the placebo group (-114.7 mL/year vs. -239.9 mL/year, $p < 0.001$ and -113.6 mL/year vs. -207.3 mL/year for INPULSIS-1 and 2, respectively). Of the nintedanib-treated patients, 29.5% had more than 10% FVC decline, as compared to 36.8% under placebo.

A total of 68 patients died in the two trials, 37 (5.8%) in the nintedanib and 31 (7.3%) in the placebo arms. Adverse events leading to treatment discontinuation were more common under nintedanib, mostly diarrheas (7.3%) and liver enzyme elevations.

Pirfenidone

Pirfenidone is the other drug approved for IPF (49;50), which is co-marketed by Intermune, Shionigi and Cipla. Pirfenidone was shown to in vitro influence TGF β and TNF activity and to inhibit fibroblast proliferation and collagen synthesis (51). While the exact mechanisms are still not sufficiently clear, pirfenidone inhibits TGF β induced transcription factors of the glioma-associated oncogene homolog (GLI) group in the downstream hedgehog (Hh) signaling pathway (52). Possibly downstream of this effect, pirfenidone suppresses MAPK signaling (53) and expression of chemokine ligand-2 (CCL-2) (54) and of inter-cellular adhesion molecule-1 (ICAM-1) (55).

The ongoing 24 week trial NCT03068234 locally performed in Shanghai, China, is testing pirfenidone primarily for its efficacy on SSc skin, with mRSS as the primary endpoint. However, interstitial lung disease is looked at in several secondary endpoints, and FVC and chest CT, in particular. Formally a phase II trial, the placebo-controlled Scleroderma Lung Study III (NCT03221257) will compare MMF with pirfenidone (801 mg tid) against MMF alone. The primary endpoint is the change in FVC; secondary endpoints include chest CTs, mRSS and SHAQ. In addition, a combined non-IPF lung fibrosis trial, RELIEF (DRKS00009822), is intended to also include patients with SSc interstitial lung disease (56).

Like with nintedanib, the hypotheses are based on the anti-fibrotic effects and similarities between SSc lung disease and IPF, and pirfenidone effects on bleomycin-induced pulmonary fibrosis (54). For IPF, the two CAPACITY trials (51) and the ASCEND trial (50) showed efficacy in reducing disease

progression. A metaanalysis of the three trials also demonstrated improved progression-free survival (49).

LOTUSS, a small, 16 week open label phase II trial of pirfenidone in patients with SSc interstitial lung disease (57), mostly (66%) in combination with MMF, mainly analyzed safety. Patients were randomized 1:1 to a faster (weekly increments) and a slower (biweekly increments) titration to the full 801 mg tid dose. Of the 32 patients in the rapid titration arm 5 (16%) stopped because of treatment-emergent adverse events, as compared to 1/31 (3%) in the slow titration arm. The most common severe treatment-emergent adverse events were fatigue (5%), diarrhea (3%) and nausea (3%). No life-threatening events occurred, and no patients died. No relevant changes in MRSS or FVC could be demonstrated. The Scleroderma Lund Study III will accordingly use the slow titration protocol.

Lenabasum

Lenabasum (formerly anabasum) is an endocannabinoid mimetic drug owned by Corbus Pharmaceuticals. Lenabasum is a synthetic analog of Δ^8 -tetrahydrocannabinol-11-oic acid, which selectively binds the CB2 receptor on activated immune cells, and thus has minimal effects on the central nervous system (58). Lower doses of lenabasum (5 mg) inhibit the neutrophil chemoattractant leukotriene B4 and inflammatory prostanoids (prostaglandin E2 and F2 α as well as Thromboxane B2), approximately equal to 15 mg prednisolon. Higher doses (20 mg) also increased lipid mediators that are thought to resolve inflammation, namely lipoxin A4, lipoxin B4, resolvin D1 and resolvin D3. Lenabasum is thought to resolve chronic inflammatory and fibrotic processes.

The one year RESOLVE-1 SSc trial (NCT03398837) sponsored by Corbus Pharmaceuticals tests 5 mg and 20 mg lenabasum against placebo. The primary endpoint is change in mRSS, but secondary endpoints include change in FVC, change in HAQ-DI and the ACR combined response index (ACR CRIS).

A 16 week double-blind phase 2 study of the efficacy of lenabasum was so far published in abstract form only (59). Of 42 patients with dcSSc included, 27 received lenabasum and 15 placebo. By ACR CRIS, anabasum treated patients had significantly greater improvement. No serious adverse events occurred.

Conclusions

There are ongoing discussions on how to best perform SSc clinical trials. Trials might better focus on specific autoantibody subsets and on early dcSSc, where prediction models derived from large cohorts could help to exclude patients with high placebo response rates (60;61). Nevertheless, current trial

protocols have been successful in showing differences, and have influence those of ongoing studies. While no final results are available yet on any of these clinical trials, it appears reassuring that so many different approaches are currently being tested in phase III randomized clinical trials in SSc patients. That potential therapies have moved to phase III evaluation is testament to the success of these agents in treating other potentially related diseases such as idiopathic pulmonary fibrosis (IPF) or in the case of tocilizumab and lenabasum success at phase II of clinical development programmes in SSc. The majority of substances are grounded in a better understanding of SSc pathophysiology, and many of them have already shown impressive efficacy in related fields. All of the drugs have in essence anti-inflammatory and secondary anti-fibrotic effects. Given both that immunosuppressive approaches, including autologous stem cell therapy, have so far only shown limited effects, and that we are not able so far to eliminate SSc autoantibodies, this kind of approach presumably has the best chance today. Accordingly, there are good reasons to hope that we will be able to offer SSc patients more effective and fairly safe medications in the near future.

Table 2. Overview of mechanisms of action in current phase III SSc trials.

Approach		Drug	Mechanism of Action	Proven Effects	
Cellular	Anti-inflammatory	Rituximab	Anti-CD20 antibody	B cell depletion IL-6 reduction	
		Tocilizumab	Anti-IL-6R antibody	IL-6R blockade Reduction fibroblast activation	
		Anti-fibrotic	Lenabasum	Cannabinoid-R CB2 mimetic	Decrease prostanoids Increase resolvins
			Nintedanib	Tyrosine kinase inhibitor	VEGF-R, FGF-R, PDGF-R activation blockade
			Pirfenidone		Inhibited fibroblast proliferation Inhibited collagen synthesis

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