Treatment of scleroderma associated ILD: Lessons from clinical trials

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Systemic sclerosis–interstitial lung disease

Systemic sclerosis (SSc) is an autoimmune disease conferring considerable morbidity and mortality. Those with associated interstitial lung disease (SSc-ILD) have the highest risk for mortality due to disease-related deaths[1,2]. The disease's impact on quality of life and healthcare costs is substantial[3,4,5]; this impact is compounded by a failure to identify a treatment that reverses the natural course of the disease. After decades of basic science and clinical research culminating in a few key clinical trials, ultimately the goal for therapy has become disease attenuation with a goal towards disease amelioration[6]. Clinical trials play a fundamental role in obtaining the safety and efficacy data of a medication; interpreting the implications and limitations of these data are critical in orphan diseases, especially when considering the rarity and heterogeneity of SSc.

In this article we review key trials in SSc-ILD (Table 1) and the lessons learned from them. Our goal is to use these data to inform current management with their associated levels of evidence in a treatment algorithm (Figures 1 & 2). We start with a few important points to consider when evaluating the results of these clinical trials.

Clinical Trials: Points to Consider

In clinical practice[7,8], treatment of SSc-ILD is generally reserved for patients exhibiting dyspnea symptoms with evidence of extensive lung disease (>20% of lung disease on high resolution chest CT (HRCT), or 10-30% in conjunction with a forced vital capacity (FVC)<70%)[9] and significant declines in pulmonary function tests (PFTs) during 12-month follow-up (FVC >10% or diffusion of carbon monoxide (DLco) >15% or both)[10]. New data from clinical trials may alter the demographics and clinical characteristics for which immunomodulatory therapy is initiated. Recently, patients with mild ILD have become the focus of study. Phase II and Phase III placebo-controlled randomized control trials[11,12] examining the effect of tocilizumab on skin thickening failed to show statistically significant benefit compared to placebo in skin thickness. However, secondary analyses found that treating these patients with early (5 or fewer years' duration from first non-Raynaud's phenomenon symptom), diffuse cutaneous, progressive disease and serologic evidence of inflammation with elevated C-reactive protein (CRP), but mild ILD (the average FVC was >80% with minimal ILD on HRCT) resulted in compelling evidence that treatment preserved lung function over 48 weeks. Another group focusing on mild ILD (defined as an FVC greater than 70%, HRCT with less than 20% pulmonary fibrosis as a percentage of total lung volume)[13] developed a prediction model of progression of mild SSc-ILD. They found 25.5% showed progression, as determined by a decrease in FVC $\geq$15%, or relative decrease in FVC $\geq$10% combined with DLCO $\geq$15%; a validation cohort found a similar rate of progression (25 of 117, or 21.4%). Notably, the true rate of progressive patients per year is likely lower, as these patients were enriched for patients with progression during the observation period. They found that those patients who progressed were more likely to benefit from immunosuppression than those who did not progress, though this study was not powered and not designed to look at treatments effects[13].

Secondly, despite well-designed prospective, placebo-controlled trials, there appears to be heterogeneity even within seemingly homogenous ILD patients. To investigate if perhaps a more robust treatment effect was being masked in the Scleroderma Lung Study-I trial (SLS-I), Roth et al., identified two mutually exclusive subsets of patients: cyclophosphamide responders and non-responders. The responders (almost half of the enrolled patients) were defined by advanced reticular disease on baseline HRCT and higher modified Rodnan skin scores (MRSS). Compared to non-responders, this subset had a

much higher FVC% predicted improvement at 18 months, suggesting that those with more severe baseline disease are most likely to respond to treatment with cyclophosphamide [14]. Identifying subsets most likely to benefit from therapy, or enriching cohort populations, is one strategy being implemented to capture maximal treatment benefit[7,13,15]. Unfortunately, treatment responders might be profoundly different depending on the type of treatment and thus cannot be generalized.

Lastly, SSc-ILD is unlike another fibrotic condition, idiopathic pulmonary fibrosis, in that SSc-ILD has slower rates of pulmonary physiology decline and mortality[16]. This presents a challenge of implementing solitary outcome measures clinically meaningful to the patient and researcher in the classical one year trial design[17,18]. Table 1 highlights the outcomes of trials in terms of their pulmonary function data, patient-reported outcomes, radiographic changes, and survival benefits. The modest benefits seen in SSc-ILD clinical trials to date may be understood as potentially limited in this regard at the cohort level, especially when only considering the primary endpoint at 1 year (e.g., FVC% change). They still might be meaningful on longer follow up, when the cumulative decline becomes clinically meaningful and is leading to increased ILD- related mortality in SSc. In 2017, the Association of Physicians of Great Britain and Ireland and the American College of Rheumatology convened to address the challenges and opportunities facing those studying connective tissue disease-ILD and highlighted the need for improved measurement tools (e.g., biomarkers and/or risk scores) to evaluate change during the trial period[19].

Notable Trials

Cyclophosphamide (CYC) is a cytotoxic alkylating agent used for the treatment of malignancy and autoimmune diseases[20]. Two prospective, randomized, placebo controlled trials[21,22] of CYC inform the 2016 European League Against Rheumatism (EULAR) recommendations for the treatment of SSc-ILD, although these were published before trials examining equally-effective, less cytotoxic options were published[23]. The Scleroderma Lung Study-I trial (oral CYC compared to placebo for one year) and the FAST study (IV CYC given monthly for 6 months in addition to 20 mg oral prednisone on alternate days, followed by azathioprine daily for 6 months compared to placebo for 12 months) both showed a modest benefit in improving the FVC%, although only SLS-I met its primary endpoint. The SLS-I study found patient-reported outcome measures (Mahler Transition Dyspnea Index, the Health Assessment Questionnaire-disability index, and the Medical Outcomes Short Form-36) showed clinically meaningful benefits in cough, functional disability, dyspnea, and mental well-being[10,12]. Oral cyclophosphamide was associated with significant adverse events (e.g., leukopenia, hematuria, neutropenia, pneumonia). Importantly, the FVC% improvement was absent 12 months after discontinuing treatment, suggesting the need for continued immunosuppression therapy[27]. These trials were harbingers for treatments to come, with a clear need for improved long-term tolerability and side effect profiles.

Mycophenolate Mofetil (MMF) is an inhibitor of inosine monophosphate dehydrogenase, ultimately impairing lymphocyte proliferation and lymphocyte migration[28]. Scleroderma Lung Study-II[29] (oral MMF 3 g/day over 2 years versus oral CYC titrated to 2 mg/kg/day for one year followed by placebo for the following year) did not meet its primary endpoint of superiority of MMF versus CYC, but found the MMF group was not inferior to those in the CYC group (change in FVC as a percentage of the predicted normal value over 2 years), with significantly fewer patients discontinuing medication in the MMF group and less adverse events (weight loss, leukopenia, thrombocytopenia). This trial provided clinicians with an equally efficacious, safer option for their SSc-ILD patients, and importantly absent the serious long-term implications CYC may pose to fertility and development of malignancy with long-term use.

Tocilizumab (TCZ) is an IL-6 receptor antagonist approved for treatment in rheumatoid arthritis, giant cell arteritis, and juvenile idiopathic arthritis. Recent Phase II and Phase III randomized control trials[11,12] in patients with early, diffuse, skin-fibrosis progressive SSc with evidence of serologic inflammatory markers (elevated CRP) and mild FVC% deficits (see Table 1) suggested attenuation of disease benefit may be derived from treatment in this population. In the faSScinate trial, although the primary endpoint of the study (mean change from baseline in the MRSS at 24 weeks) did not differ significantly between the study drug and placebo, there was strong evidence of benefit in the study drug group on the exploratory endpoint FVC percentage (fewer patients had a decline in percent predicted FVC at 48 weeks). In the focuSSced Phase 3 trial, secondary endpoint analyses showed preservation of lung function in the study drug group compared with a strong worsening of FVC in placebo, over 48 weeks. These studies raise the possibility of targeting early and subclinical ILD [mean FVC was 84% ±15% in the placebo arm, 80% ±14% in the active treatment arm, mean DLCO was 77% ±19% in the placebo arm, 74% ±19% in the active treatment arm at baseline] and preventing progressive and largely irreversible SSc-ILD in this specific patient population.

Rituximab (RTX) is a B-cell targeted therapy with mounting evidence to suggest benefit in patients with SSc-ILD. Daoussis et al., 2017 treated patients with SSc-ILD over the course of 7 years; those in the RTX group had higher FVC% compared to baseline; those in the control group showed a decreased FVC% compared to baseline)[30]. In a recent open label RCT[31] in patients with early diffuse cutaneous SSc-ILD who were anti-SCL-70 positive and treatment naïve showed significant improvement in patient's receiving RTX versus IV CYC in terms of FVC over 6 month follow-up (61.3% to 67.5% versus 59.3% to 58.1%). Importantly, this therapy has yet to demonstrate benefit in a double-blind randomized control trial; a recent observational study of SSc-ILD patients (n=146) matched on skin and lung disease to those not receiving RTX therapy, could not show a benefit[32].

Nintedanib and pirfenidone are approved treatments for idiopathic pulmonary fibrosis. The SENSCIS trial demonstrated statistically significant effects on the primary endpoint FVC. In a panel of 576 patients with SSc-ILD (HRCT involvement >10% and no upper limit of FVC%) receiving at least one dose of the study drug or placebo, with patients on a stable dose of MMF or methotrexate for at least 6 months (patients could also receive concomitant prednisone 15 milligrams per day), half were randomized to nintedanib 150mg twice a day or placebo. The primary endpoint was change in FVC in mL's over a 52-week period. The effect was 41 ml difference in the one-year study. The benefit seen in reduction of FVC decline falls short of the minimal clinically important difference (MCID) as expected in this one year trial with a mostly unselected SSc-ILD cohort and progression of only 91 ml in the placebo group, which is also below the MCID [26]. Patients in the treatment arm were more likely to have diarrhea and GI side effects. Scleroderma Lung Study-III (SLS-III) (clinical trials.gov: NCT03221257) is an on-going clinical trial using anti-fibrotic therapy, recruiting an estimated 150 participants using a combination of MMF and pirfenidone. The primary endpoint is changing predicted FVC percentage over 18 months; secondary end points include change in the modified Rodnan skin score, the extent of fibrosis and total ILD on HRCT, the percent predicted DLCO, transitional dyspnea index, and other patient reported outcomes.

All the above trials have been performed over a 24 to 52-week period [apart from SLS-II, that was a 104 week trial] and our interpretation is that the short therapy is not sufficient to attenuate the decline in lung function. Observational cohorts have suggested that the largest decline in FVC happens in the first few years after the onset of SSc and then the FVC decline tapers off although there are individual

differences. Longer-term follow up from ongoing trials such as SENCIS and other cohorts will help identify the duration of treatment required with current therapies.

Hematopoietic autologous stem cell transplant has been studied in three key trials: Autologous Stem Cell Systemic Sclerosis Immune Suppression Trial (ASSIST), Autologous Stem Cell Transplantation International Scleroderma (ASTIS), and Scleroderma Cyclophosphamide or Transplantation (SCOT). This therapy is reserved for patients with severe, treatment-refractory SSc(-ILD). The SCOT trial demonstrated improved event free survival compared to cyclophosphamide as well as specific SSc-ILD improvement (greater proportion of patients with a relative increase of FVC by $\geq$10%, and fewer patients with a relative decrease by $\geq$10%). Notably, these were long-term trial with a long follow up to measure differences between outcomes.

Management strategies: Goals of treatment in 2019

In terms of diagnosis, all patients with SSc should receive HRCT at their baseline evaluation to determine the presence of ILD, despite a delay in adopting this practice pattern[33,34]. Additionally, all patients require evaluation for cardiac involvement (myocardial involvement and pulmonary hypertension) at the initial visit. Pulmonary function tests lack the sensitivity and specificity relative to HRCT in diagnosis of SSc-ILD, however monitoring every 4-6 months in the first 3-5 years of disease onset provides valuable information about disease trajectory[35–37].

In terms of treatment, there are different strategies for management of ILD and current authors have employed these in their practices. The variation in practice strategies in key SSc centers underline that more data are needed on the sequence of treatment initiation, which patients to select for which treatment, and whom to treat; a formal consensus development is required to propose solicited recommendations. The following statements therefore should be considered as preliminary and the opinion of single authors of this manuscript.

Strategy 1: The management of SSc-ILD may begin with stratifying patients in terms of the severity of lung disease[38]. We have operationally defined subclinical ILD as those patients who are asymptomatic with regard to ILD, have minimal-to-mild ILD on HRCT, FVC% or DLco% above the lower limit of normal and if more than 1 PFT is available, show no decline in FVC >10% or FVC $\geq$5% to <10% with $\geq$15% decline in DLco[39], and have no desaturation on oximetry with hall walk attributable to ILD. Patients with clinical ILD are defined as those with symptoms attributable to ILD in conjunction with mild-to-severe ILD on HRCT and persisting PFT deficits greater than those listed above.

Figure 1 outlines this strategy: those with subclinical ILD and low risk for progressive disease may be monitored with serial PFTs and routine symptom assessment, especially within the first 5 years of SSc diagnosis[40]. Those with subclinical ILD at present but with a high risk trajectory for developing progressive lung disease (e.g., early diffuse cutaneous disease with progressive skin involvement, positive SCL-70 antibody, or elevated C-reactive protein) should be initiated on immunomodulatory therapy that can be TCZ [11,12,41,42] or MMF based on our unpublished experience.

Those patients with clinical ILD should be treated with immunomodulatory therapy; we recommend the use of MMF or CYC depending on individual needs of the patient (e.g., fertility and hormonal concerns in pre-menopausal women, concerns of co-occurring malignancy, liver and renal insufficiency, co-existing disease involvements and immune profile). Induction therapy for those with primary lung disease (with

no other systemic active signs and symptoms) is typically with MMF (compared to CYC, it has similar efficacy and a better tolerability profile). The advent of nintedanib's FDA-approval for SSc-ILD offers the possibility of providing benefit as an additional therapy on background MMF, or may be considered as first line therapy with ILD predominant disease without skin or other active aspects of SSc.

For those with multi-organ involvement with treatment-refractory lung disease, select patients without significant cardiac involvement, and excluding smokers, autologous hematopoietic stem cell transplant or early referral to transplant center for further evaluation may be indicated. In this population, few good data exist to direct therapy choices: we consider, before establishing refractoriness, the addition of nintedanib or RTX or transition to CYC, although no evidence-based consensus of last two recommendations have been determined. Consideration for novel agents still in phase II of clinical trials may be used on a compassionate basis.

Strategy 2: Another strategy for management is strictly adhering to the published evidence and is aiming at prevention of progression independent of the extent of SSc-ILD (figure 2). Accordingly, patients fulfilling the inclusion criteria of the TCZ trials (early, diffuse, inflammatory, skin-progressive) should be treated with TCZ where available. Autologous stem cell transplantation might be an option for this patient group if there is a progression despite TCZ. Patients in whom ILD is the leading manifestation and therapy of skin, arthritis etc., is not required, should be treated with nintedanib. Clinically, this is a very different population compared to the TCZ cohort with minimal overlap. Mycophenolate mofetil is available for patients where neither the criteria for TCZ nor nintedanib apply or when these medications are not available. Cyclophosphamide can be given for a maximum of one year when MMF is not available. There is currently no published evidence whether upfront combination therapy is more efficient than sequential therapy of MMF and nintedanib, but based on the SENSCIS study, sequential combination therapy could be considered for patients with high risk of progression or where progression has occurred under monotherapy. Safety consideration may drive this step-up strategy. There are no data available for efficacy and safety of combination therapy with TCZ and nintedanib, which therefore should only be used in an experimental setting.

In this strategy aiming at prevention of progression and damage, patients at risk of progression should be treated before worsening has occurred and before patients become symptomatic. Indeed, patients with ILD frequently have FVC values within normal values and are clinically unremarkable[43]. Waiting until progression has occurred already allows major damage to the lungs which is likely difficult to revert in SSc-ILD. It is however appreciated that the current models predicting worsening are imprecise and need further validation and fine-tuning.

In addition to choosing a treatment strategy, focus should be placed on improving other outcomes that matter to the patient (e.g., retard the progression of skin thickening, occupational hand therapy to prevent joint contractures, vasodilator treatment for Raynaud's Phenomenon or digital ulcerations, and concomitant treatment of pulmonary arterial hypertension). All patients with SSc-ILD should receive annual influenza and age-appropriate pneumococcal vaccination, control of gastroesophageal reflux disease, pulmonary rehabilitation, and use of supplemental oxygen when appropriate[44].

Conclusion/summary

The pathogenesis of SSc-ILD is multifactorial and an effective therapeutic strategy achieving disease reversal has been elusive. Immunosuppressive treatments have led to modest benefit; the lack of

efficacy in terms of reversing disease progression may be a combination of limitations to cohort enrichment (accurately assessing subsets of SSc-ILD patients with the highest likelihood of benefit from treatment), the efficacy of medical therapy, or challenges associated with clinical trial outcome measure design.

The beneficial effects of immune suppression appear to be less straightforward than initially considered: benefit has been seen in both subclinical disease (as defined by minimal–mild ILD on HRCT with FVC and DLco% greater than the lower limit of normal and in the absence of respiratory symptoms attributable to ILD) as well as those with extensive fibrotic disease. This might depend on the specific immunosuppressive treatments and molecular targets modified by them. Advances in understanding the pathophysiology of fibrotic lung disease have led towards combination therapy of immunosuppression with other disease modifying agents and strategies. The benefits of all treatment strategies including combination therapies will need to be weighed against side effects. There is limited evidence to support a mortality benefit in SSc–ILD treatment, with the exception of autologous hematopoietic stem cell transplant, which might be due to the long-term follow up in the stem cells transplantation trials able to detect mortality differences.

Three hopeful goals remain: 1) subclinical patients may be accurately identified early in their disease course, monitored for disease progression or identified as being high risk and initiated on preventive therapy, 2) clinical patients may receive prevention therapies to attenuate disease progression, 3) progressive patients should receive therapy prior to catastrophic parenchymal lung loss.

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Table 1: Clinical trials in scleroderma–ILD

Trial/ Medication	Population/ Study Design	Primary Endpoint	FVC%/ DLco%	HRCT Findings	Function/ Quality of
FAST[22] Active Arm: IV CYC for 6 months (600 mg/m2/month for 6 months + 20 mg oral prednisolone on alternate days followed by azathioprine [2.5 mg/kg/day]) (N=22) Comparator Arm: Placebo for 12 months (N=23)	SSc-ILD Baseline FVC% in the Active Arm: 80.1% (±10.3) Comparator Arm: 81.0% (±18.8) Randomized double-blind placebo controlled trial with 12 month follow-up	Percent predicted FVC at 12 months, after adjusting for baseline FVC	Significant improvement in FVC% favoring CYC: +4.19% (-0.57 to 8.95) P=0.08 No significant difference in DLCO% between arms.	6 of 15 patients treated with CYC showed improvement (reduced coarseness and/or extent of disease), compared with 3 of 15 patients in the placebo arm.	No signific dyspnea s follow-up.
SLS-I[21] Active Arm: Oral CYC for 12 months (2mg/m2/day for 12 months) (N=79) Comparator Arm: Placebo for 12 months (N=79)	SSc-ILD Baseline FVC% in the Active Arm: 67.6(±1.5) Comparator Arm: 68.6(±1.5) Randomized double blind placebo controlled trial with 12 month follow-up	Percent predicted FVC at 12 months, after adjusting for baseline FVC	Significant improvement in FVC% favoring CYC: +2.53% (0.28 to 4.79) P<0.03 No significant difference in DLCO% between arms.	CYC arm showed less worsening of fibrosis on serial HRCT scans compared to placebo.[45]	Cough fre significant the CYC gr after disco not 12 mo discontinu Breathless improved months w dyspnea i Disability attenuate months w scores: -0.
SLS-II[29] Active Arm: Oral MMF (target dose 1500 milligrams twice daily) for 24 months (N=69) Comparator Arm: Oral CYC (2 mg/kg/day) for 12 months followed by placebo for 12 months for 12 months (N=73)	SSc-ILD Baseline FVC% in the Active Arm: 66.5(±8.3) Comparator Arm: 66.5(±9.9) Randomized double-blind paralleled group trial with 24 month follow-up	Percent predicted FVC at 24 months, after adjusting for baseline FVC	Improvement in FVC% in both MMF and CYC at 24 months: +2.19% (0.53 to 3.84) +2.88% (1.19 to 4.58) No difference between the two treatment arms. DLCO% decreased less during the course of MMF treatment than CYC treatment.	Quantitative ILD involving the whole lung was significantly reduced by an average of 2.51% (-4 to -1.03) over 24 months. There was no significant difference between MMF and CYC arms[48].	Breathless improvem minimal c changes in CYC arms, between-t difference with Trans index: +1. Leicester Questionn frequency significant months fo data at th no differe treatment

ASTIS[50] Active Arm: Non-myeloablative autologous HSCT with CYC 4g/m2 and G-CSF (mobilization) and CYC 200mg/kg + rabbit ATG (conditioning) (N=79) Comparator Arm: IV CYC (750mg/m2 monthly for 12 months) (N=77)	Diffuse SSc (Onset <4 years); 87% had SSc-ILD Baseline FVC % in the Active Arm: 81.7% (±19.3) Comparator Arm: 81.1% (±17.6) Open-label, Randomized, parallel-group trial with 48 month follow-up	Event-free survival, defined as time from randomization until the occurrence of death or persistent major organ failure at 2 years.	Significant improvement in FVC % favoring HSCT arm: +6.3 (±18.3) Comparator Arm: -2.8 (±17.2) P=0.004 No significant difference in DLCO% between arms.	In a subset of the HSCT arm, N=20 responders (stabilization or improvement in FVC >10% and DLCO >10%) showed significantly decreased high attenuation value areas and improved total lung volumes[51].	The physi score of th 4.0; differ −10.9 to − HAQ–DI (- difference to0.73].
SCOT[52] Active Arm: Myeloablative autologous HSCT with G-CSF (mobilization) and CYC 120mg/kg) + equine ATG (conditioning) with total body irradiation (800cGy, lung and kidney shielding) (N=36) Comparator Arm: IV CYC (750mg/m2 monthly for 12 months) (N=39)	Diffuse SSc (Onset <4 years); 97% had SSc-ILD Baseline FVC% in the Active Arm: 74.5 (±14.8) Comparator Arm: 73.8 (±17.0) Phase II, Open label, Randomized Trial with 54 month follow-up	Global rank composite score comparing participants with each other on the basis of a hierarchy of disease features assessed at 54 months.	Significant improvement favoring HSCT: 36% improved (relative increase of FVC by >10%) Comparator Arm: 23% improved	Quantitative ILD for the whole lung showed a significant improvement for HSCT patients (-7% [±2]), while the CYC group did not improve (0% [± 5]) (p= 0.024). Similarly, for the whole lung, the QLF improved (-1% [± 1]) while the CYC group worsened (+3% [± 3]) (p= 0.047)[53]	Of the eve those rece were mor improved quality of HAQ-DI (6 the CYC ar (73% vers arm).
faSScinate[11] Active Arm: Subcutaneous TCZ (162 mg weekly) for 48 weeks (N=43) Comparator Arm: Placebo for 48 weeks (N=44)	Mild SSc-ILD (HRCT were not performed in all patients) Mean Baseline FVC% was 80% ±14% Comparator arm: 82%±13% Phase II randomized placebo controlled trial with 48 week follow-up	Mean change in modified Rodnan skin score from baseline to 24 weeks.	Reduced FVC% decline in active arm at 48 weeks: -2.6% (-5.2 to -0.1) Comparator arm: -6.3% (-8.9 to -3.8) P=0.037) No significant difference between	N/A	Patient-re did not di between a exception analogue over place

			arms in mean DLCO% predicted.		
focuSSced[12] Active Arm: Subcutaneous TCZ (162mg weekly) for 48 weeks (N=104) Comparator Arm: Placebo for 48 weeks (N=106)	Mild SSc-ILD Mean Baseline FVC 80% ±14% Comparator arm: 84% ±15% Phase III randomized placebo controlled trial with 48 week follow-up	Mean change in modified Rodnan skin score from baseline to 24 weeks.	Significantly Reduced FVC% decline in active arm at 48 weeks: -0.6% (-5.3 to 3.9) Comparator arm: -3.9% (-7.2 to 0.6) P= 0.0015 No difference in the DLCO percent predicted .	N/A	N/A
MYILD[54] Active arm: Oral MMF (1000 milligrams twice daily) for 6 months (N=20) Comparator arm: Oral placebo for 6 months (N=21)	Mild SSc-ILD Mean Baseline FVC % was 81.71%±9.35% Randomized double blind placebo controlled trial with 6 month follow-up	Comparison of the change in FVC% after 6 months of therapy with MMF or placebo.	No improvement in FVC% in MMF arm -1.79± 7.32 compared to placebo 1.34% ±4.47. No significant difference between arms in mean DLCO percent predicted.	N/A	SF 36 scor improved
Rituximab vs CYC[31] Active arm: RTX 1000mg x2 vs. CYC 500mg/m2 every 4 weeks x6 months (N=30) At Wk 24, CYC switched to AZA or MMF; RTX continued q6mo 1000mg/dose.) (N=30)	SSc-ILD Baseline FVC% in the RTX Arm: 61.3(±11.28) Comparator Arm: 59.5(±12.96) Randomized open label trials with 6 month follow-up	FVC% predicted at 6 months	Significant improvement in the FVC% predicted in the rituximab group at 6 months RTX: 61.30 to 67.52 CYC: 59.25 to 58.06; the mean difference in FVC % was in favor of RTX (9.46; 3.01, 15.90) P=0.003.	N/A	N/A
SENCSIS[55] Active arm: 150 milligrams of Nintedanib twice daily (N=288) Comparator arm: Placebo twice daily (N=288)	SSc-ILD Baseline FVC% in the Nintedanib Arm: 72.4(±16.8) Placebo Arm: 72.7(±16.6)	Annual rate of decline of FVC in millimeters per year at 52 weeks	The annual rate of decline in FVC at week 52 was -52.4mL (-1.4%) in Nintedanib group and -93.3mL (-2.6%) in the placebo group.	N/A	No effect on patient outcomes

					Randomized double blind placebo controlled with 52 week follow-up

Figure 1: Treatment Strategy 1

Figure 1 here

Legend:

University of Michigan Scleroderma Program treatment algorithm based on data from clinical trials and expert opinion

Acronyms

ILD = interstitial lung disease

dcSSc = diffuse cutaneous systemic sclerosis

CRP = C-reactive protein

SCL-70 = Anti-topoisomerase I antibody

PFT = pulmonary function tests

HRCT = high resolution chest computed tomography

MMF = mycophenolate mofetil

Definitions of subclinical and clinical ILD

Subclinical ILD: asymptomatic with regard to ILD, minimal-to-mild ILD on HRCT, FVC% or DLco% above the lower limit of normal and if more than 1 PFT is available, there should be no decline in FVC >10% or FVC $\geq$5% to <10% with $\geq$15% decline in DLco, no desaturation on oximetry with hall walk attributable to ILD.

Clinical ILD: mild-to-severe ILD on HRCT, persisting PFT deficits, and in whom symptoms are attributable to ILD.

Strength of Recommendations[56]

1A From meta-analysis of randomized controlled trials

1B From at least one randomized controlled trial

2A From at least one controlled study without randomization

2B From at least one type of quasi-experimental study

3 From descriptive studies, such as comparative studies, correlation studies or case-control studies

4 From expert committee reports or opinions and/or clinical experience of respected authorities

Figure 2: Treatment Strategy 2

Figure 2 here

Legend:

University of Zurich Scleroderma Program treatment algorithm based on data from clinical trials and expert opinion

Acronyms

SSc = Scleroderma

ILD = interstitial lung disease

HSCT = hematopoietic stem cell transplant

MMF = mycophenolate mofetil

Strength of Recommendations[56]

1A From meta-analysis of randomized controlled trials

1B From at least one randomized controlled trial

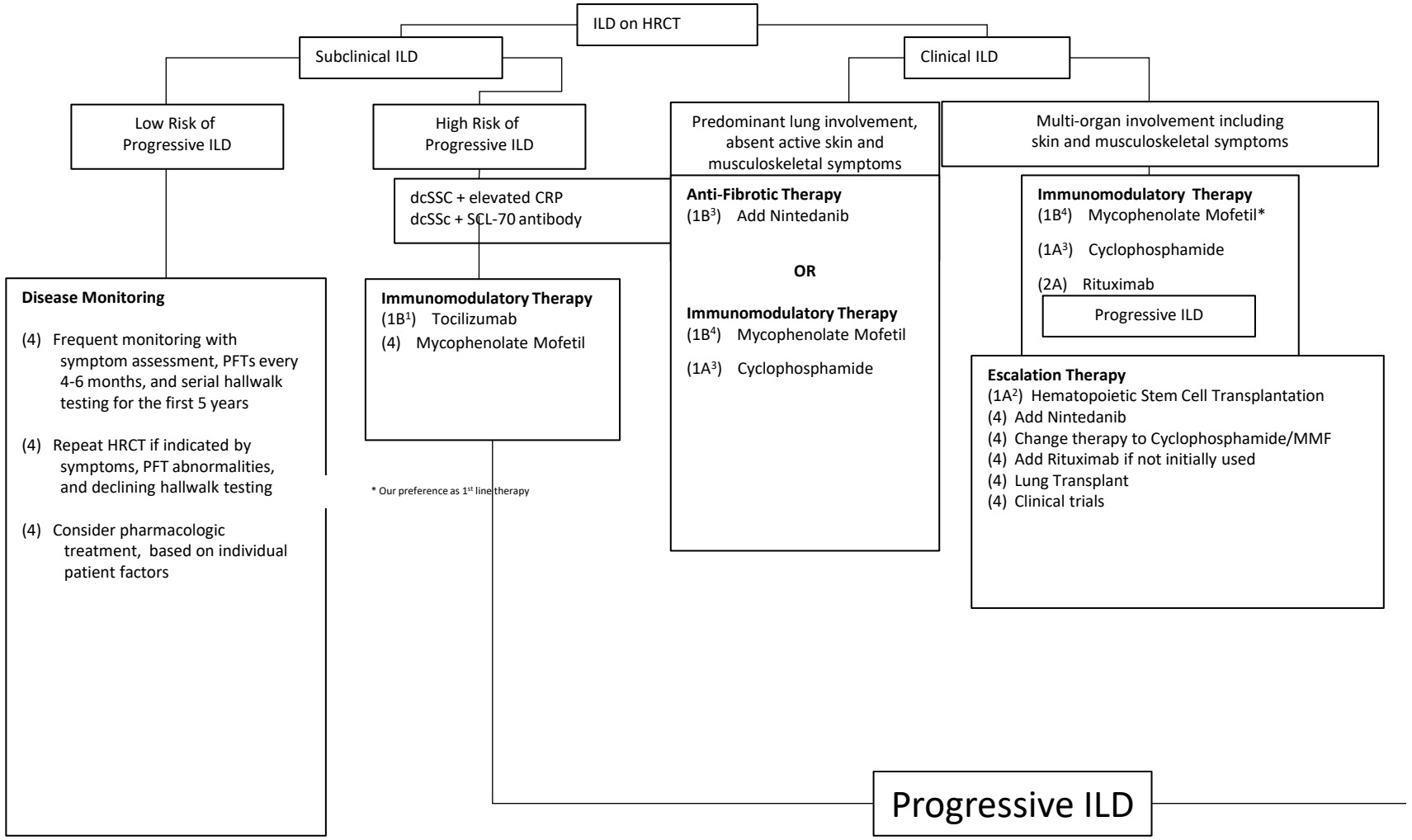
2A From at least one controlled study without randomization

2B From at least one type of quasi-experimental study

3 From descriptive studies, such as comparative studies, correlation studies or case-control studies

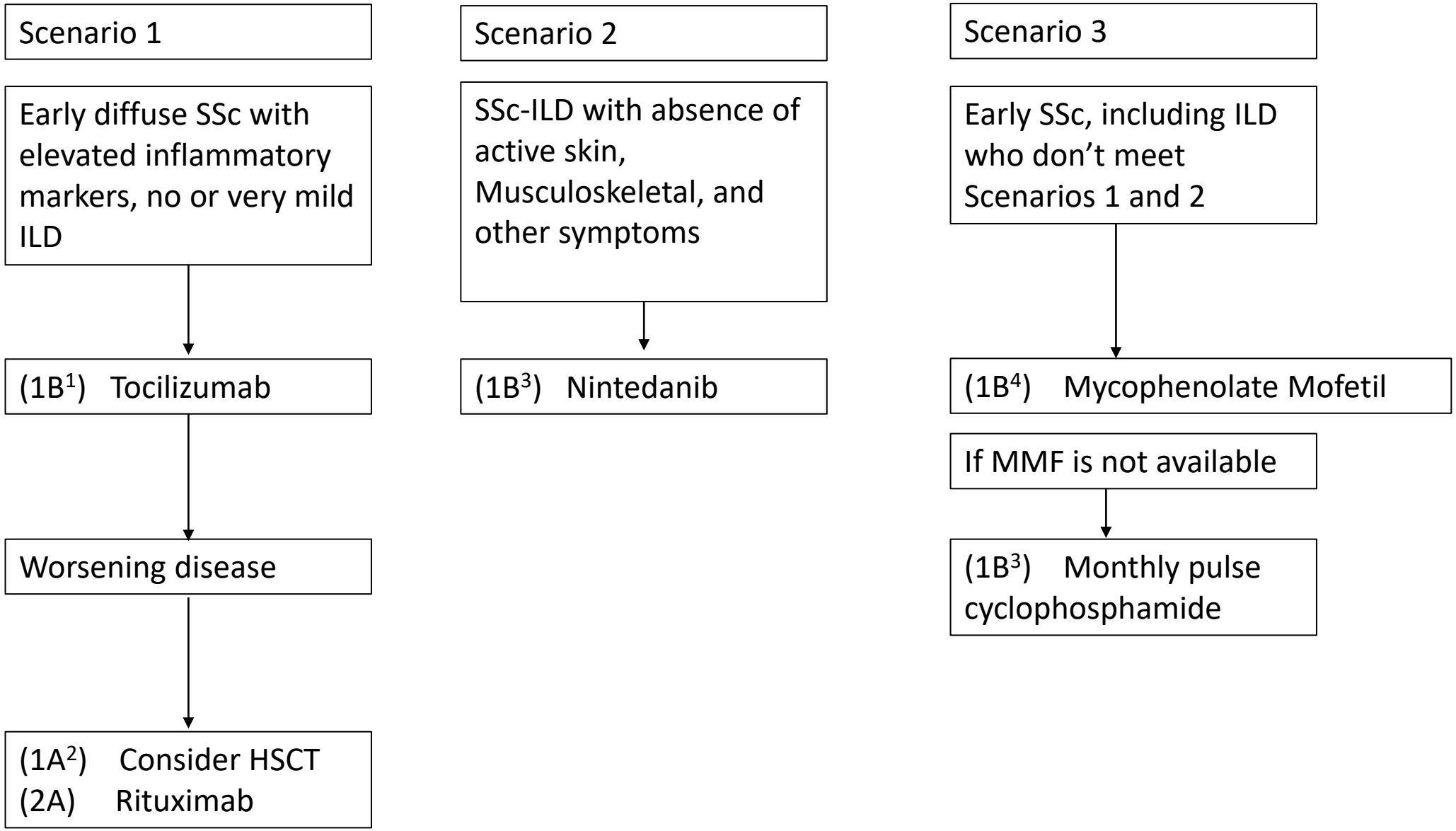
4 From expert committee reports or opinions and/or clinical experience of respected authorities

Figure 1



[1] Evidence based on two RCTs with positive secondary or exploratory endpoint and a large effect size
[2] Evidence based on three RCTs
[3] Evidence based on one primary endpoint positive RCT
[4] Evidence based on a primary endpoint negative RCT but similar effects compared to CYC and accumulating evidence from observational studies and SENSCIS subanalysis

Figure 2



[1] Evidence based on two RCTs with positive secondary or exploratory endpoint and a large effect size

[2] Evidence based on three RCTs

[3] Evidence based on one primary endpoint positive RCT

[4] Evidence based on a primary endpoint negative RCT but similar effects compared to CYC and accumulating evidence from observational studies and SENSCIS subanalys