



Management of Interstitial Lung Disease in Systemic Sclerosis

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Disclaimer

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Points for Discussion

- Brief overview of Systemic Sclerosis
- Interstitial Lung Disease in Systemic Sclerosis
 - How to diagnose
 - How to Treat
 - How to Monitor

Systemic Sclerosis (SSc) or Scleroderma



- Greek words
 - Scleros – thickened
 - Derma – skin
- The first report in 1753, by Carlo Curizo – 17 year old patient – extensive tension and hardness of skin all over her body





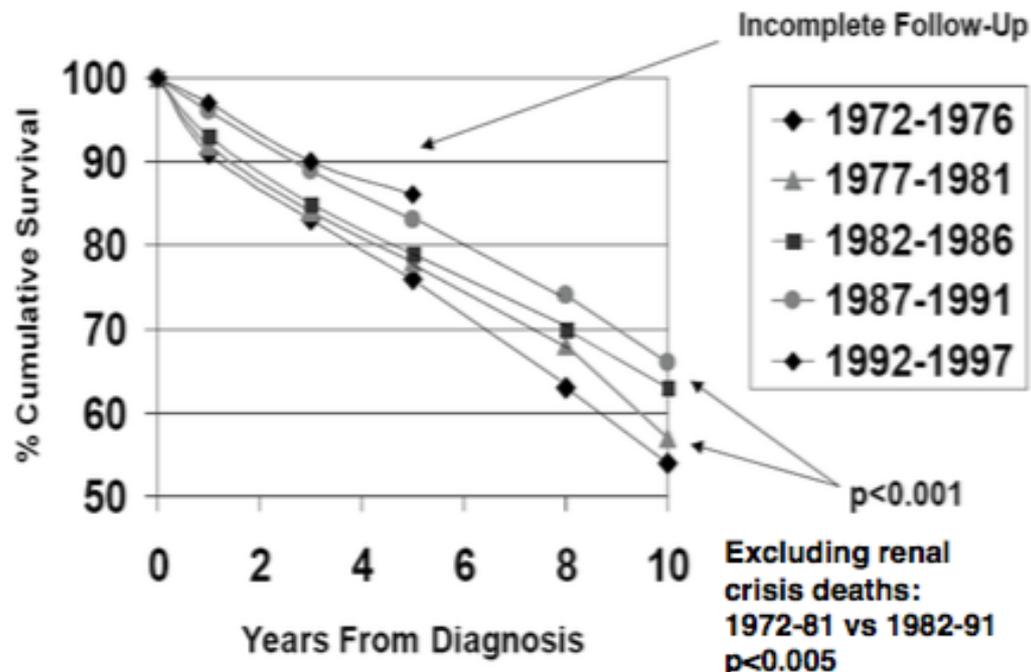
Burden

Worst 10 year survival among autoimmune diseases

10 yr survival:

- SSc
 - 54% (1970's) to
 - 66% (1990's)
- SLE 90%
- ANCA assocted vasculitis 75%

Figure 1. Survival of patients with systemic sclerosis between 1972 and 2002.



Pittsburg cohort Ann Rheum Dis Feb 2007

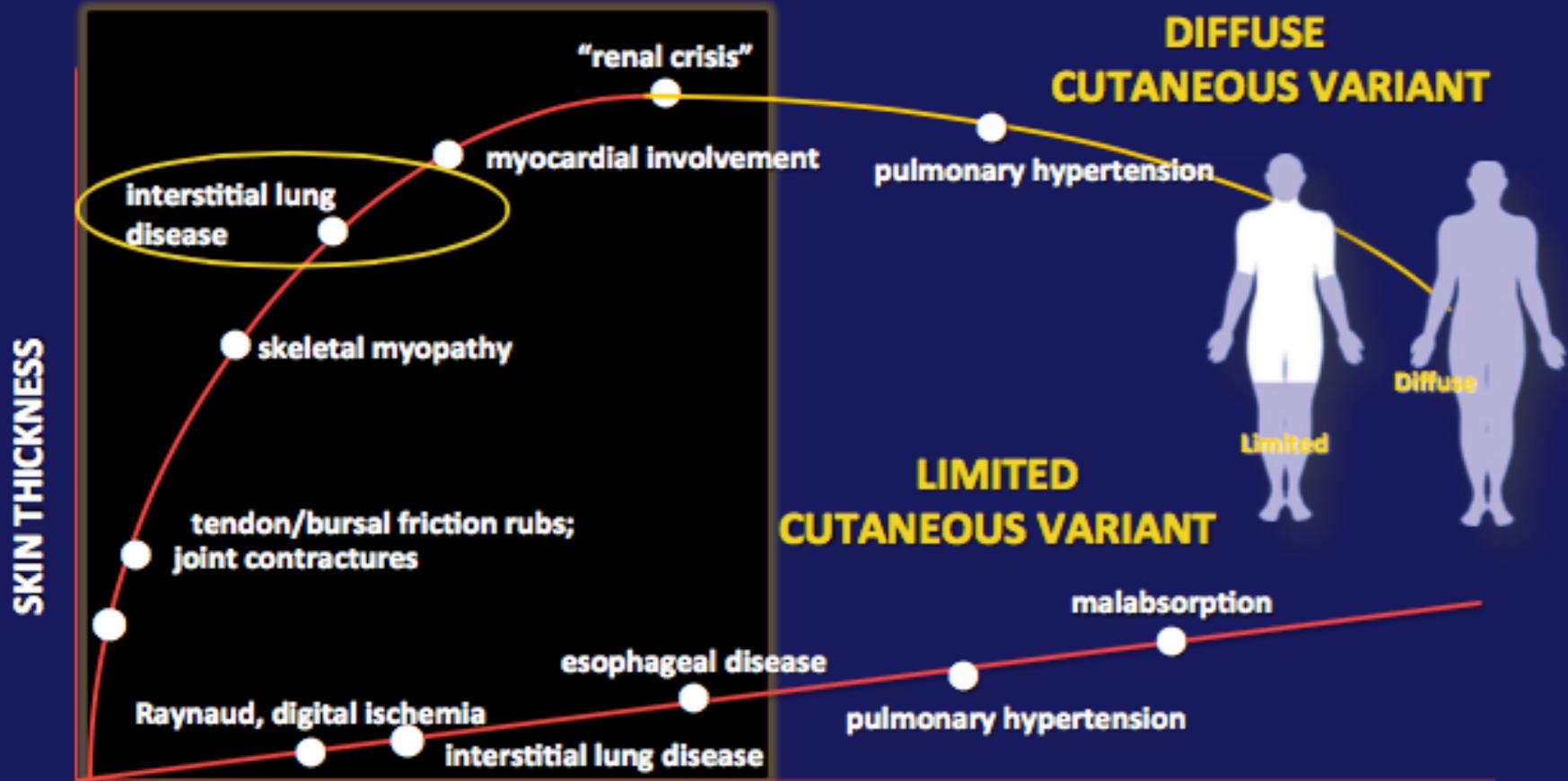


Number of Admissions at the Department of Rheumatology, Yangon Specialty Hospital

- 288 (2014)
- 309 (2015)
- 383 (2016)
- 355 (2017)



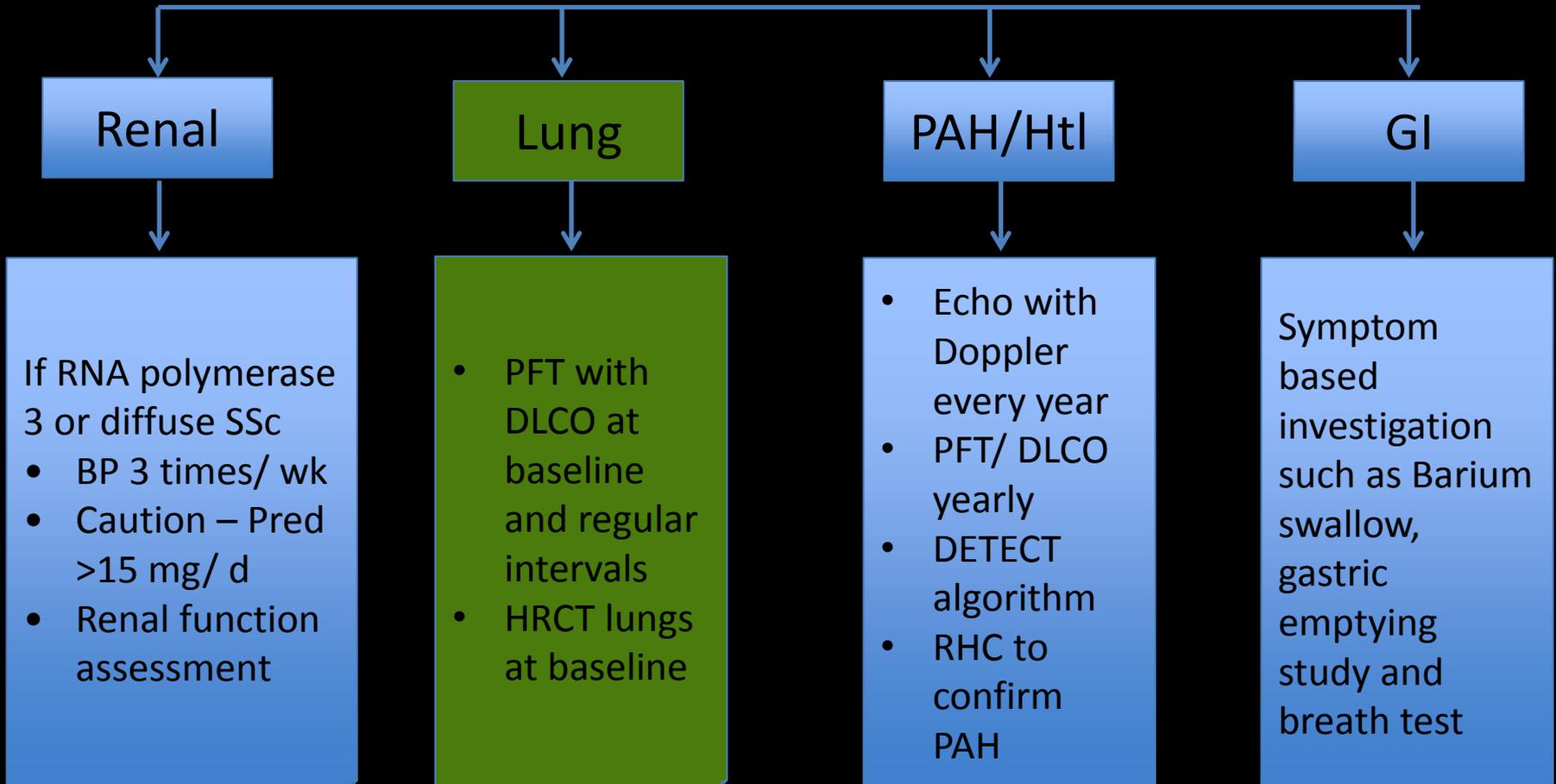
Usual Timing of Problems in Systemic Sclerosis



2-5 years after first non RP symptom/sign

Provided by Thomas Medsger

Screening for Internal Organ Involvement



Systemic Sclerosis related Interstitial Lung Disease (SSc-ILD)

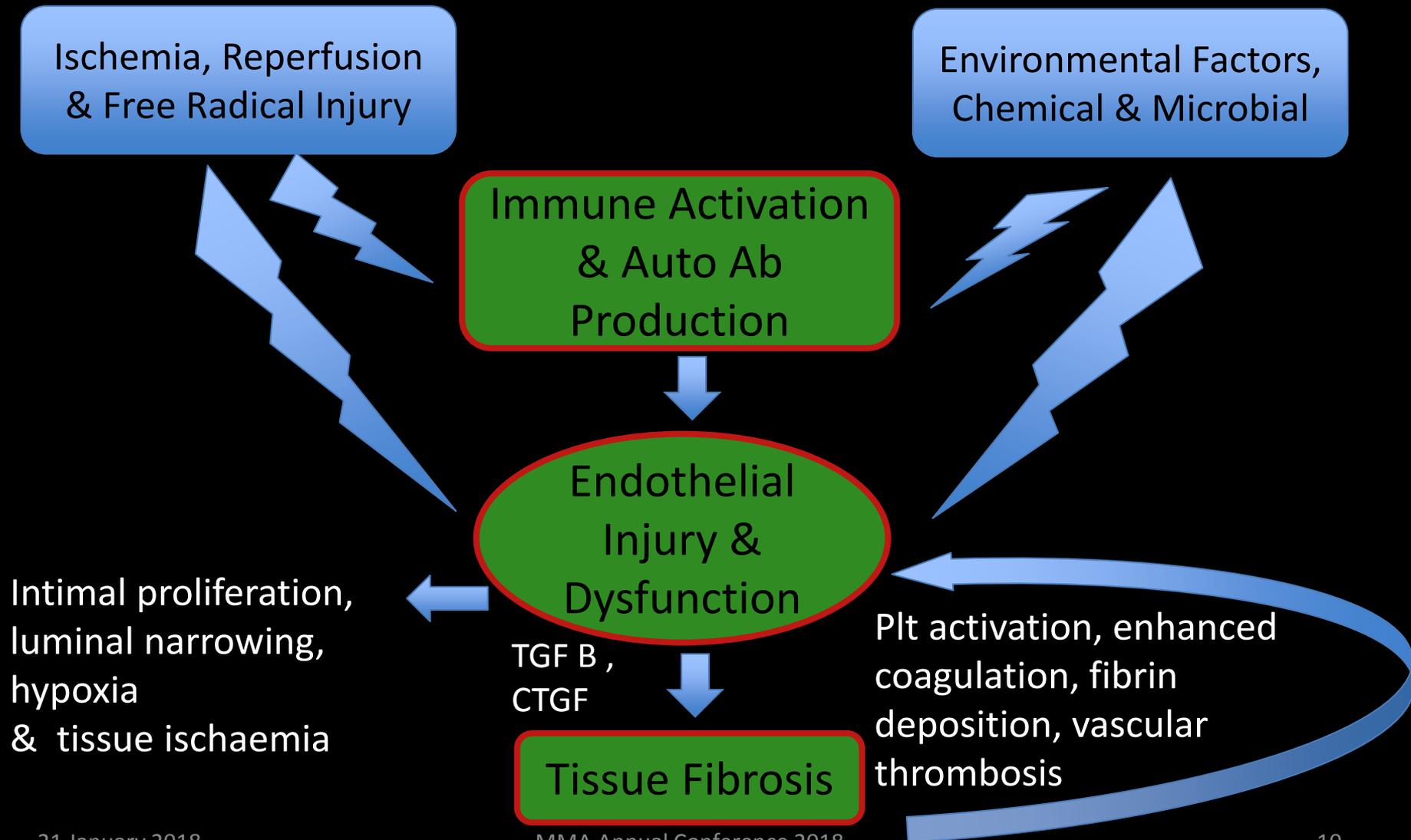


- Heterogeneous group of diseases characterized by inflammation and / or fibrosis of the lung parenchyma which eventually lead to impairment of gas exchange respiratory failure and subsequently death.





Pathogenesis – The Triad





Classification

- Usual interstitial pneumonia (UIP)
- Non-specific interstitial pneumonia (NSIP)
 - Cellular, fibrosing and mixed patterns
- Organizing pneumonia (OP)
- Diffuse alveolar damage (DAD)
- Respiratory bronchiolitis (RB)
- Desquamative interstitial pneumonia (DIP)
- Lymphoid interstitial pneumonia (LIP)

Adapted from American Thoracic Society/ European Respiratory Society (2002)



Epidemiology

- Prevalence depends on patient selection and diagnostic methods used
 - 88 – 91% of patients (by HRCT)
- 40% of patients – restrictive lung disease
- 10 – 15% of patients – severe lung disease (FVC <50%)
- Most frequent pulmonary complication
- Major cause of mortality (30% of deaths)



Risk Factors

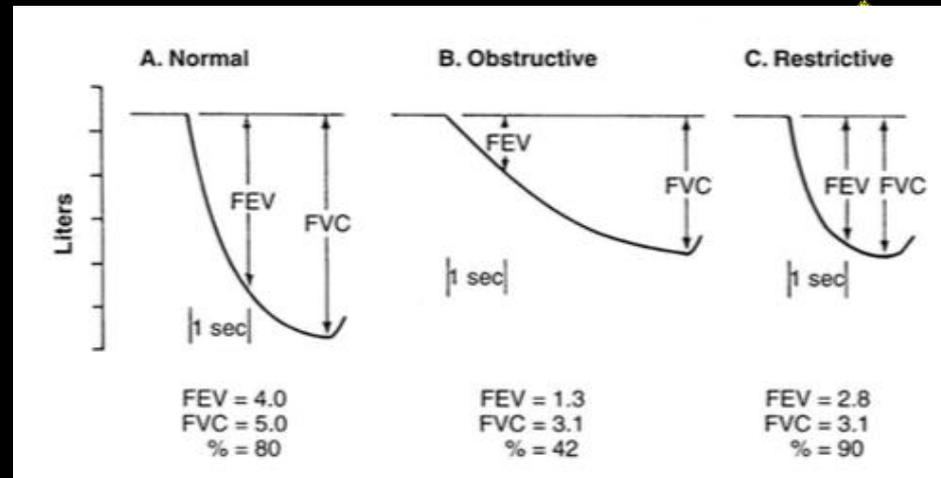
- African American ethnicity
- Male
- High modified Rodnan Skin Score
- Early disease
- Presence of cardiac involvement
- Serum CK level
- Anti-topoisomerase Ab
- Absence of anti-centromere Ab
- Anti-U11/ U12 RNP Abs



Evaluation

- Pulmonary function tests
- Imaging assessment
- Six minute walk test – Oxygen desaturation
- Cardiopulmonary exercise testing – prognosis
- Bronchoalveolar lavage – granulocytosis – poor prognosis
- Lung biopsy – not usually indicated

Role of PFTs



- Detection of ILD and other pulmonary complications
- Revealing the nature of pathophysiological processes in the lungs
- Assessment of the severity and progression of ILD
- Assessment of prognosis
- Assessment of treatment efficacy

Role of imaging



Early



Advanced

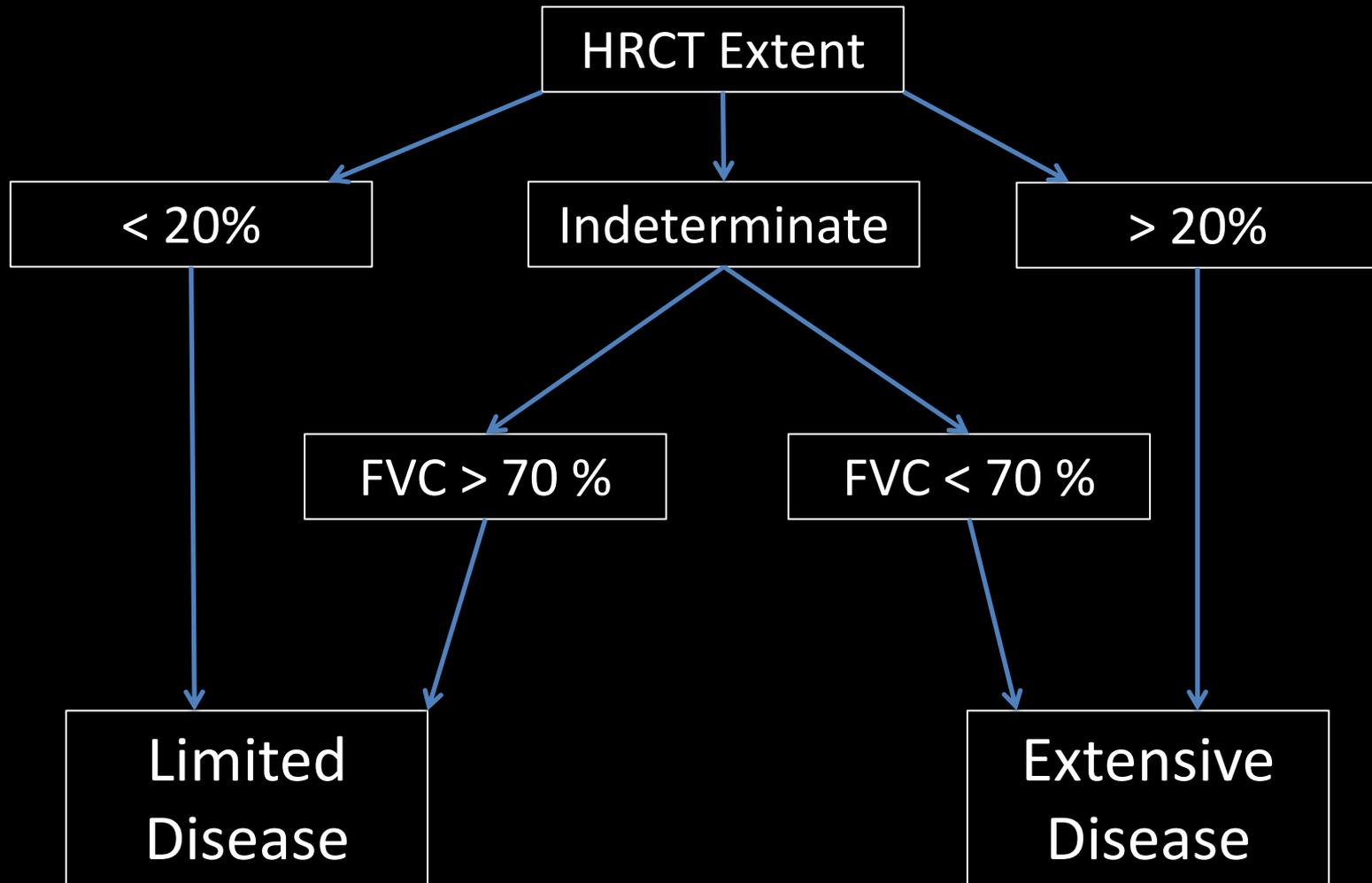
- Detection of ILD
- Exclusion of other lung diseases
- Assessment of the extent of ILD
- Identification of patient more likely to respond to treatment
- Assessment of treatment efficacy
- Identification of site for bronchoalveolar lavage/ lung biopsy
- Need prone images

Pulmonary Assessment and monitoring

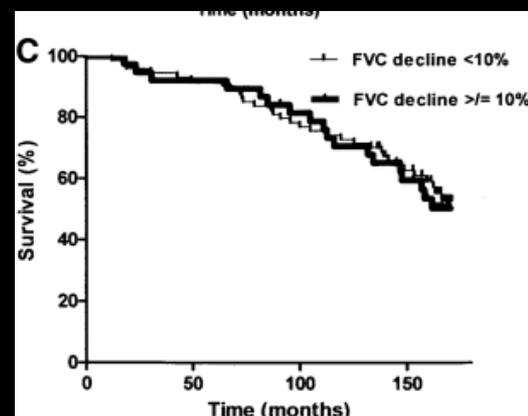
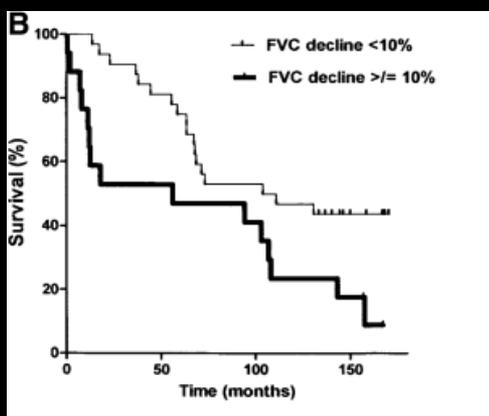
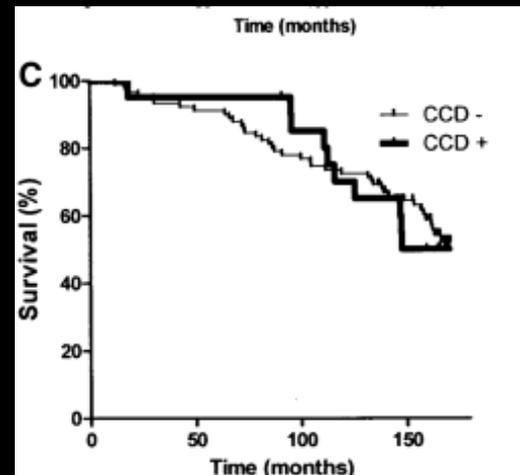
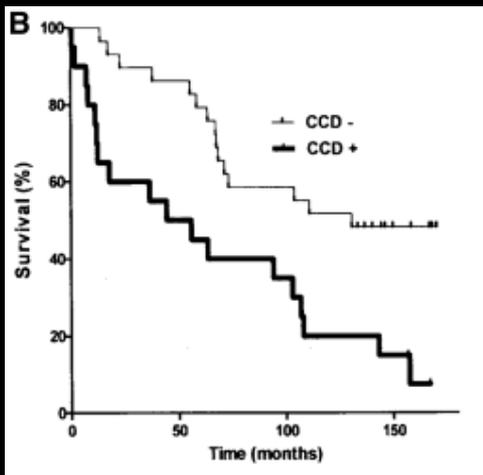


	Category	Assessment	Time
Baseline	Early SSc	Spirometry & DLCO	Within 12 mo
	FVC or DLCO < 80 % of predicted	HRCT lungs	Within 12 mo
Follow up	Early SSc	Spirometry & DLCO	Every yr for 5 yr
	Interstitial Lung Disease	Spirometry & DLCO	Every yr until stable
	New dyspnoea at exertion	Spirometry & DLCO	Within 6 mo
	New dyspnoea at exertion &/or FVC or DLCO < 80% for the 1 st time	HRCT Lungs	Within 6 mo

Staging system to assess the risk of progression in SSc-ILD



Short-Term Pulmonary Function Trends Are Predictive of Mortality in Interstitial Lung Disease Associated With Systemic Sclerosis



Extensive Lung Fibrosis

Limited Lung Fibrosis

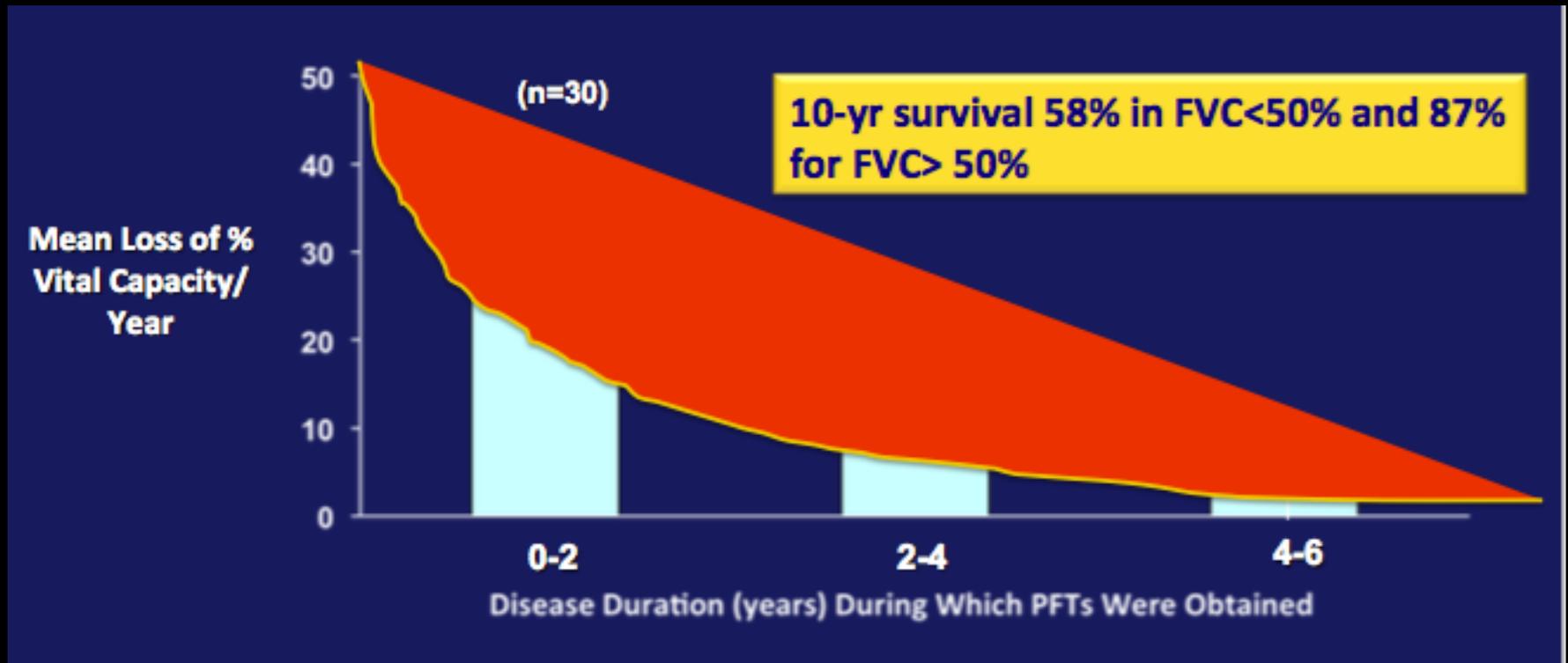


Predictor of Prognosis

- Low baseline PFTs (FVC, DLCO)
- Greater HRCT score
- Extent of fibrosis
- Decline in PFTs
- Desaturation on exercise
- Presence of PHT
- Early or diffuse SSc
- Anti-topoisomerase Abs
- Anti-U11/ U12 RNP Abs
- CRP
- Granulocytosis in bronchoalveolar lavage fluid



Mean loss of vital capacity over time



- In patients with severe pulmonary fibrosis, (FVC < 50%) the most rapid decline occurs in the first 4 years of disease

Steen VD et.al, Arthr Rheum. 1994;37 : 1283 - 1289



Scope of Management

- General measures
- When to treat
- How to treat



General Measures

- Addressing co-morbidities: GERD, PHT, CVD
- Pulmonary Rehabilitation
- Immunization
- Smoking cessation
- Antibiotics : short course (stand-by), long term
- PCP prophylaxis
- Oxygen therapy
- Bone protection



When to treat

- Baseline characteristics
 - Age, functional status, preferences
 - Risk of toxicity
 - Likelihood of response: “Reversibility”
 - Severity of ILD
 - Extra-thoracic manifestations
- Disease behavior prior to referral:
 - Recent decline: objective and subjective measures
 - Duration of symptoms
- If one decides not to treat, the importance of longitudinal disease behaviour



When to Treat

Patient with SSc and Dyspnoea within 7 years of first signs or symptoms attributable to SSc with

- FVC % decline of 10% in the last 12 months ¹
- FVC decline of 5 – 9 % and DLCO 15% or more in the last 12 months ¹
- FVC % predicted 70% or less at the time of presentation ²
- Moderate fibrosis on HRCT (>25%) or total lung involvement of > 20% ^{2, 3}

1. Goh, et al. Arthritis Rheum 2017
2. Tashkin D, et al. NEJM 2006
3. Goh, et al. AJCCRM 2008



Likelihood of reversibility

- Previous response to steroids?
 - Dose of steroids used
 - Which symptoms improved: breathlessness Vs generally feel better
 - Objective evidence of improvement eg. Lung function
- Bronchoscopy and lavage (if performed)
 - Lymphocytosis (experience from idiopathic interstitial pneumonia)



Likelihood of reversibility

Underlying HRCT pattern

- UIP, cellular NSIP tend to be steroid responsive.
- Pure Organizing pneumonia (OP) is frequently admixed with NSIP
-

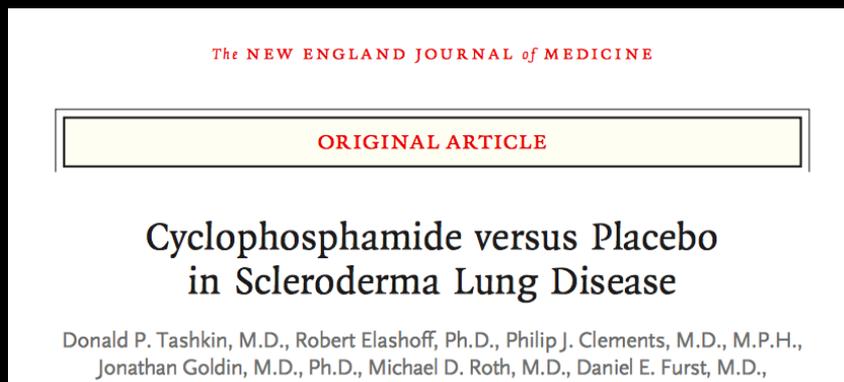


Available Choices of Immunosuppressants and Biologicals

- Cyclophosphamide
- Mycophenolate Mofetyl
- Azathioprine
- Methotrexate
- Calcineurin inhibitors – Cyclosporine & Tacrolimus
- Steroids
- Biologics – Anti-TNF, Anti-CD20,
- Stem cell transplant



Cyclophosphamide



- Scleroderma Lung Study (SLS)
- One year of oral cyclophosphamide in patients with symptomatic scleroderma-related interstitial lung disease had a significant but modest beneficial effect on lung function, dyspnea, thickening of the skin, and the health-related quality of life. The effects on lung function were maintained through the 24 months of the study.

N Engl J Med 2006;354:2655-66.

Cyclophosphamide



ARTHRITIS & RHEUMATISM
Vol. 54, No. 12, December 2006, pp 3962–3970
DOI 10.1002/art.22204
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A Multicenter, Prospective, Randomized, Double-Blind, Placebo-Controlled Trial of Corticosteroids and Intravenous Cyclophosphamide Followed by Oral Azathioprine for the Treatment of Pulmonary Fibrosis in Scleroderma

Rachel K. Hoyles,¹ Ross W. Ellis,¹ Jessica Wellsbury,¹ Belinda Lees,¹ Pauline Newlands,¹ Nicole S. L. Goh,¹ Christopher Roberts,² Sujal Desai,³ Ariane L. Herrick,⁴ Neil J. McHugh,⁵

- **treatment of pulmonary fibrosis in SSc with low-dose prednisolone and IV CYC followed by AZA stabilizes lung function in a subset of patients with the disease. Therapy was well tolerated with no increase in serious adverse events.**



Mycophenolate Mofetyl



HHS Public Access

Author manuscript

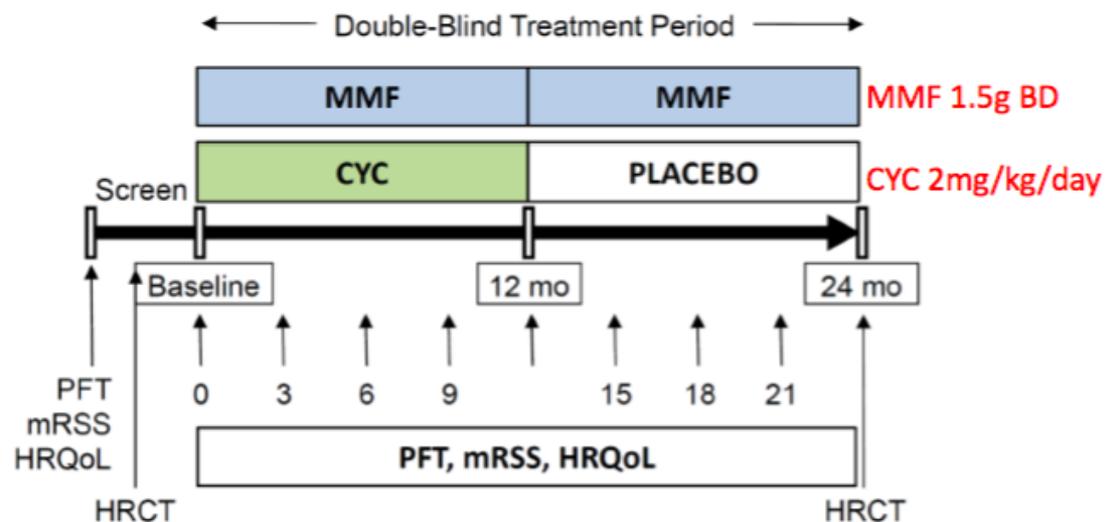
Lancet Respir Med. Author manuscript; available in PMC 2017 September 01.

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Lancet Respir Med. 2016 September ; 4(9): 708–719. doi:10.1016/S2213-2600(16)30152-7.

Mycophenolate Mofetil versus Oral Cyclophosphamide in Scleroderma-related Interstitial Lung Disease: Scleroderma Lung Study II (SLS-II), a double-blind, parallel group, randomised controlled trial

Prof. Donald P Tashkin, MD¹, Prof. Michael D Roth, MD,
Daniel E Furst, MD¹, Prof. Dinesh Khanna, MD², Prof. J



Lancet Respir Med. 2016 September ; 4(9): 708–719. doi:10.1016/S2213-2600(16)30152-7.

Mycophenolate Mofetyl – SLS II



Treatment of SSc-ILD with MMF for two years or CYC for one year both resulted in significant improvements in pre-specified measures of lung function, dyspnea, lung imaging, and skin disease over the 2-year course of the study. While MMF was better tolerated and associated with less toxicity, the hypothesis that it would have greater efficacy at 24 months than CYC was not confirmed.



Other Immuno-suppressants

- Azathioprine
 - Limited evidence, used for 6/12 after CYC in FAST trial,
- Methotrexate
 - Improvement in skin and global assessment
- Cyclosporin & Tacrolimus
 - Limited data
- Steroids
 - Doses over 15 mg per day – risk of scleroderma renal crisis



Biologics

- Rituximab
 - Small studies
 - Stabilized or Improved lung function
- Anti- TNF
 - Limited data
 - Etanercept – no significant effect
- Tocilizumab (Anti-IL6)
 - Promising results



Other Treatments

- Stem cell transplant
 - Improved lung function
- Lung Transplant
 - Survival at 1 year – 80 – 93 %, 3-5 year – 50 – 70 %

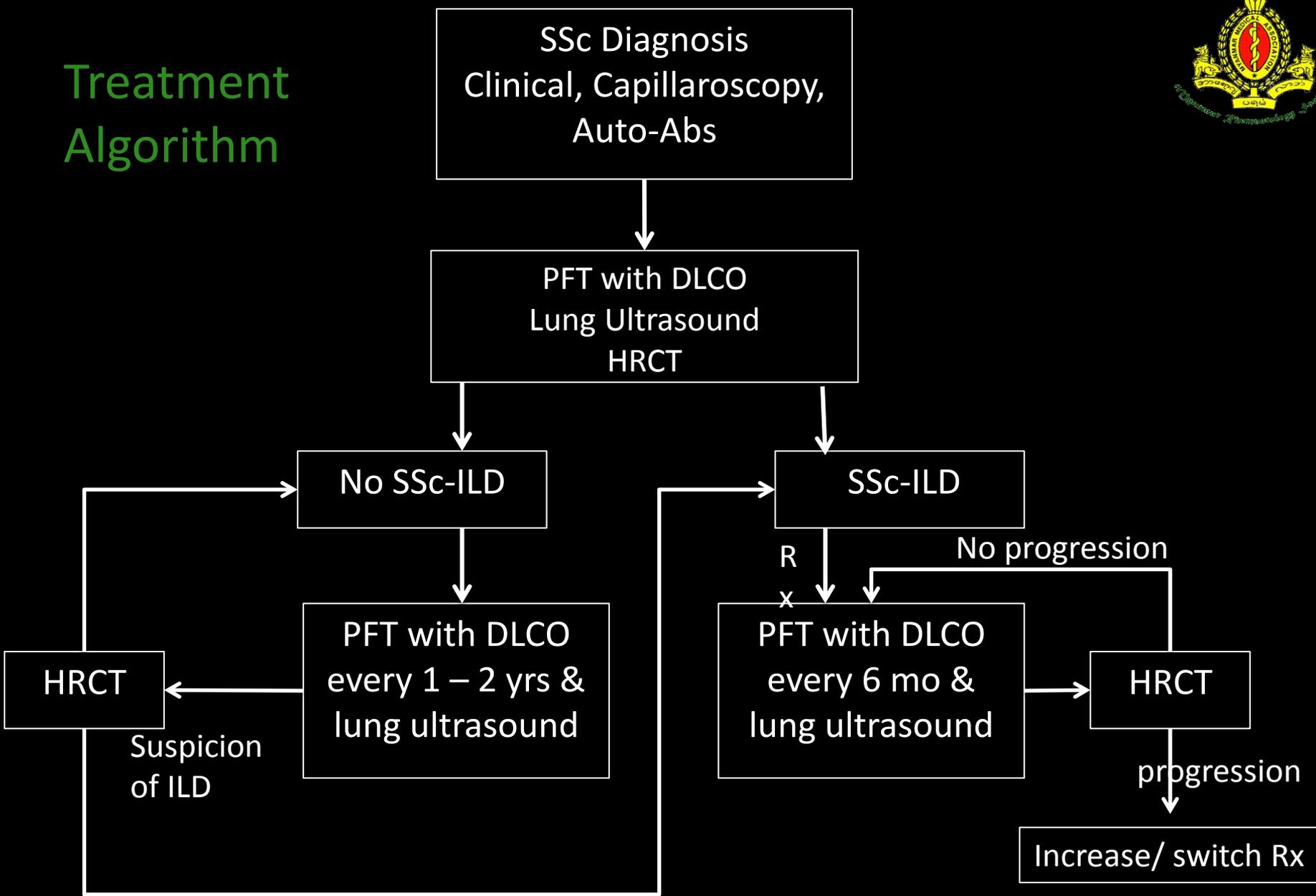


Anti- Fibrotics

- Trials are assessing if addition of an anti-fibrotic therapy with MMF will be superior to MMF alone
 - 3 large anti-fibrotic trials
 - * Pirfenidone MOA – likely TGF beta inhibition
 - * Nintedanib , MOA – Tyrosine kinase inhibitor
 - Abituzumab MOA – integrin inhibitor
- * Approved in IPF



Treatment Algorithm



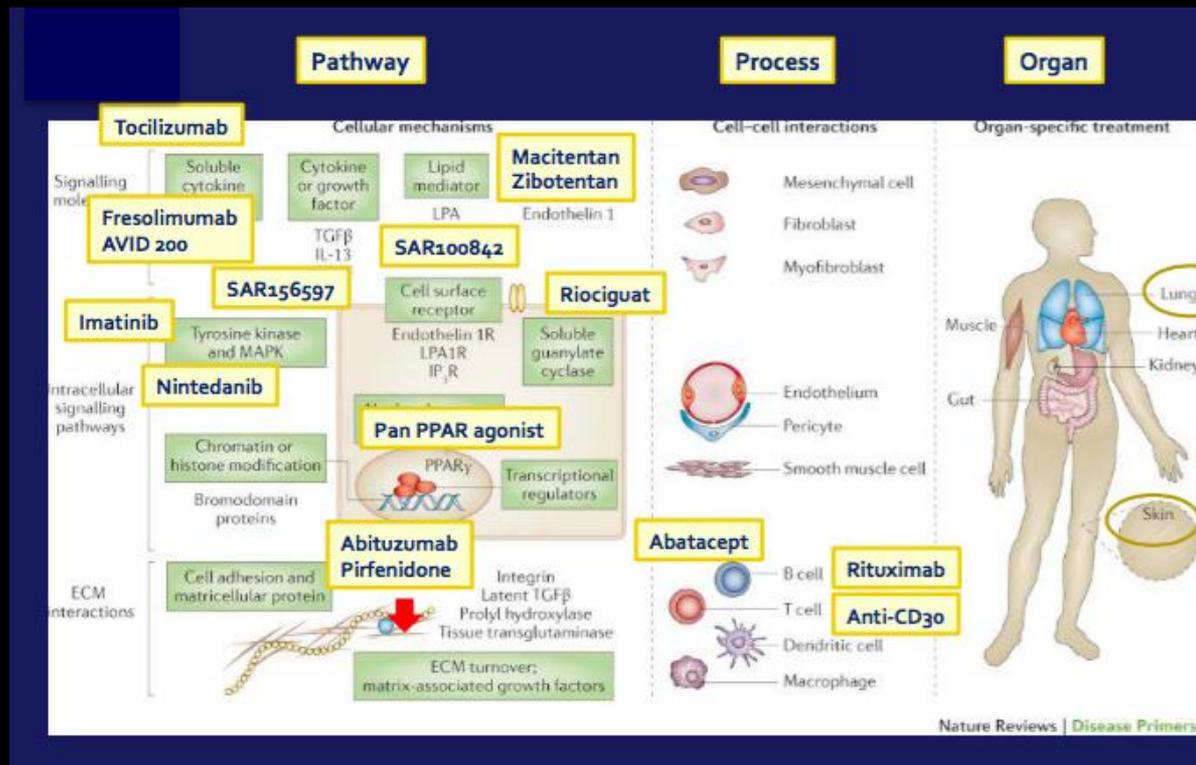


Current management perspective for SSc-ILD

- Immunosuppressive treatments are superior to placebo
- MMF is probably as effective as oral cyclophosphamide and better tolerated
- Treatment effect of immunosuppression is modest and does not tackle the underlying fibrotic process
- Immunosuppression provided current standard of care for patients considered to be at risk of significant or progressive lung fibrosis in scleroderma.

Ongoing Trials

- Abatacept
- Tofacitinib
- Anti-IL4/ IL 13 inhibitor
- Anti-oncostatin M
- Anti-CD 30
- Anti-TGF beta 1 & 3 isoforms
- Pan-PPAR gamma agonist





Take-home message

- 80 – 90 % have ILD on HRCT
- Occur earlier in the disease (generally first 2 – 4 years)
- Inflammation and rapid loss of FVC occur primarily in first 4 – 6 years and then quietly subside.
- Further losses of FVC are usually very indolent
- Largely irreversible once fibrotic
- Immunosuppressive treatments are superior to placebo

Thank you

