Lung Involvement in Rheumatic Disease

Should we forget immunosuppressive drugs?

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Conflit of Interest Disclosure

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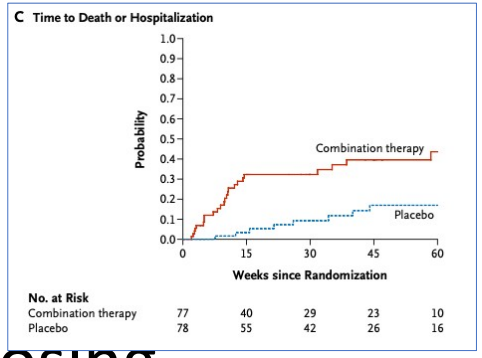
The connective tissue diseases (CTD) in question

- Rheumatoid Arthritis (RA)
- Sjögren's Syndrome
- Systemic sclerosis (SSc)
- Myositis
- Lupus
- Mixed Connective tissue disease
- Interstitial pneumonia associated with autoimmune features (IPAF)

- Abnormalities of cellular and humoral immune function, loss of tolerance to self antigens
- Immunologically mediated disorders characterised by inflammation

➢ therapeutic approach in clinical practice is usually based on the use of steroids and immunosuppressive drugs

Why ask this question for CTD-ILD?



- Inflammatory ILD vs. **Fibrosing ILD**
- Immunosuppressors have a deleterious effect in Idiopathic Pulmonary Fibrosis
- "Positive" Randomized Controlled Trial with antifibrotic in fibrosing ILD
  - In IPF
  - In non IPF including CTD-ILD

- Presence of ILD and its progression have a major prognostic impact

Raghu, NEJM 2012; Solomon, ERJ 2016; Volkmann, Ann Rheum Dis 2019; Nasser, ERJ 2

Behaviour and pattern in CTD-ILD

Some patients have limited or stable lung involvement whereas in others, lung disease progresses inexorably.

Inflammatory

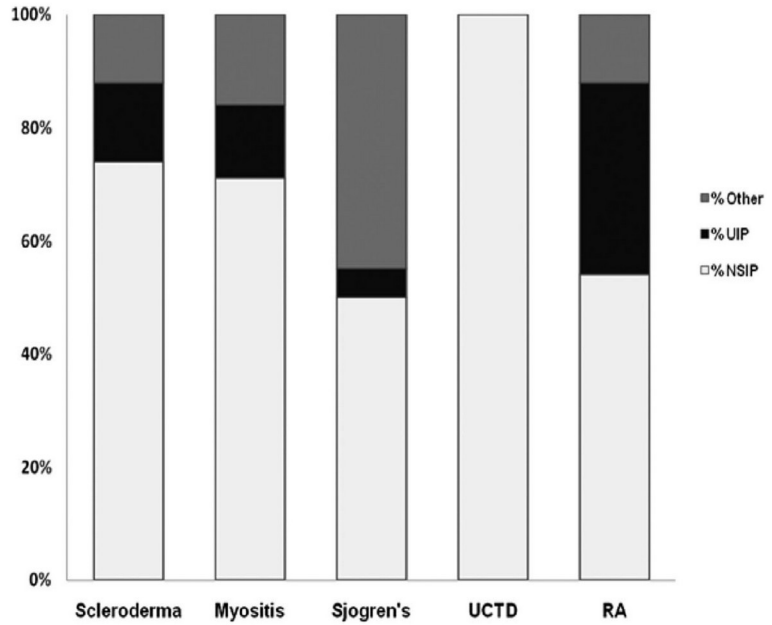
- Subacute involvement:
  - Organising pneumonia
  - NSIP/OP
  - Cellular Nonspecific interstitial pneumonia (NSIP)
- Fulminant involvement
  - Diffuse alveolar damage inaugural or acute exacerbation
  - Diffuse alveolar haemorrhage

Other

- Subtle radiographic changes

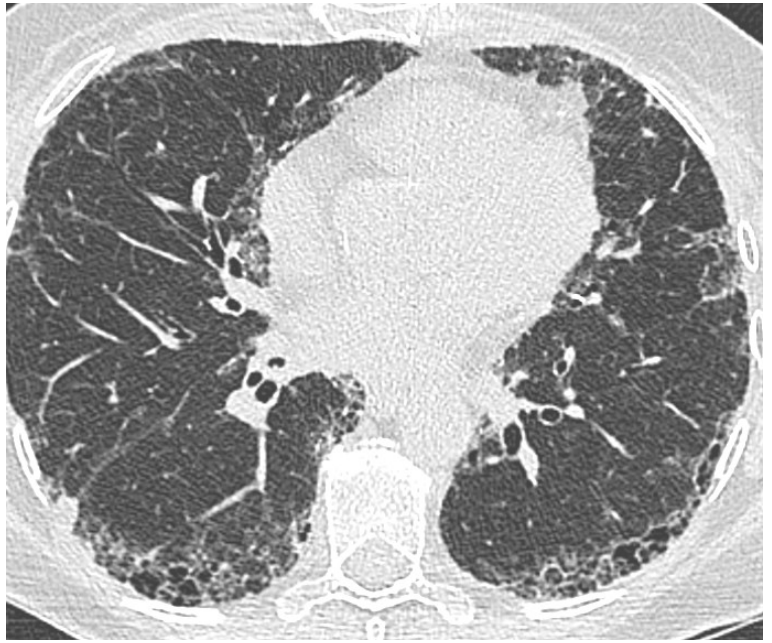
Fibrosing

- Fibrosing NSIP
- Usual interstitial pneumonia (UIP)
- Unclassifiable pneumonia



Kim, Chest 2009

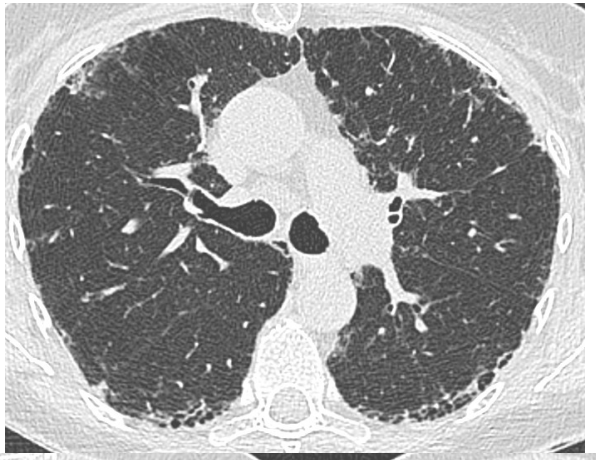
Mrs C.

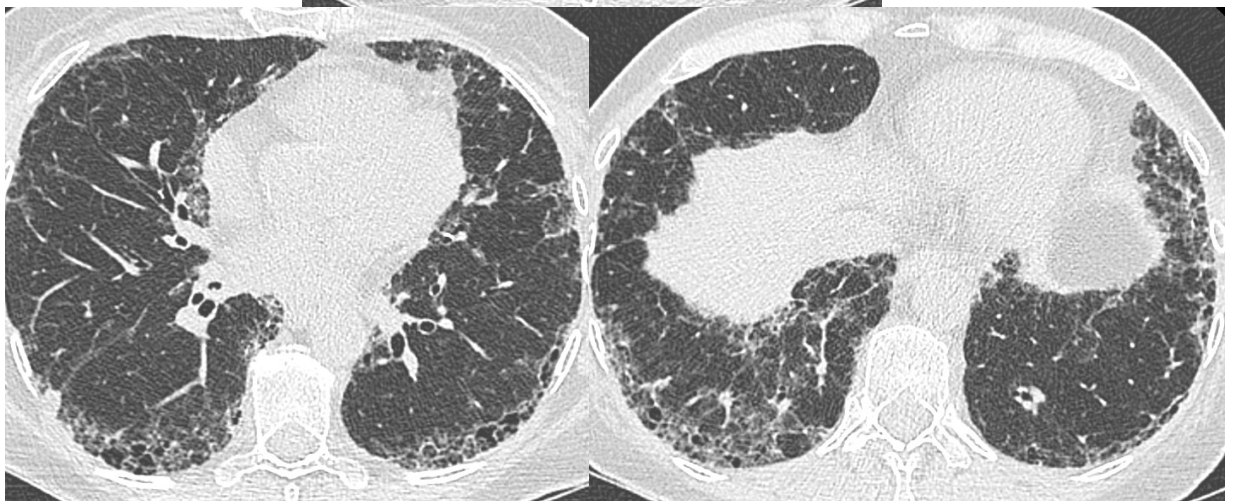


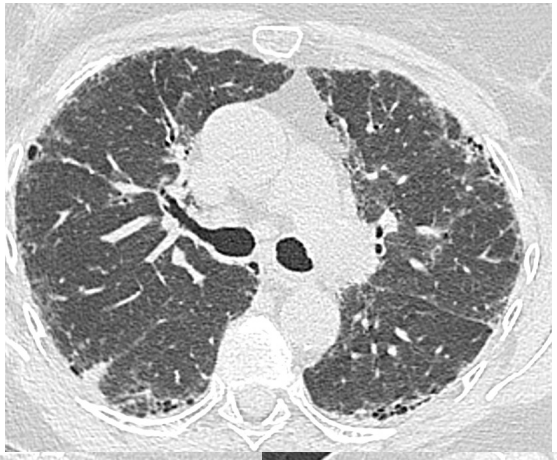
- A 59 years-old woman
- Former smoker, 35 pack-years
- ILD associated Sjogren's syndrome known since 2012
- HRCT pattern: UIP

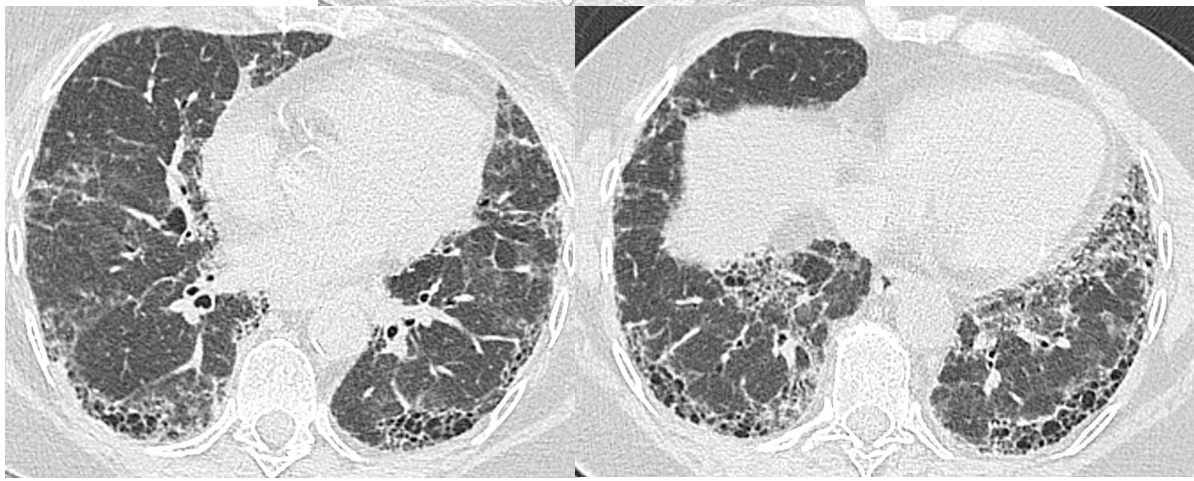
- 2018:
  - Corticosteroid (10 mg) prescribed for cough. No frank efficacy and bad tolerance (anxiety)
- 2020:
  - Progressive clinical worsening (increased dyspnoea from mMRC 1 to mMRC 2)

	2019	07/2020	12/2020
FVC, L **(%)**	2,25 **(75)**	1.82 **(63)**	1,69 **(59)**
DLCO, %	69	50	ND









What do you suggest?

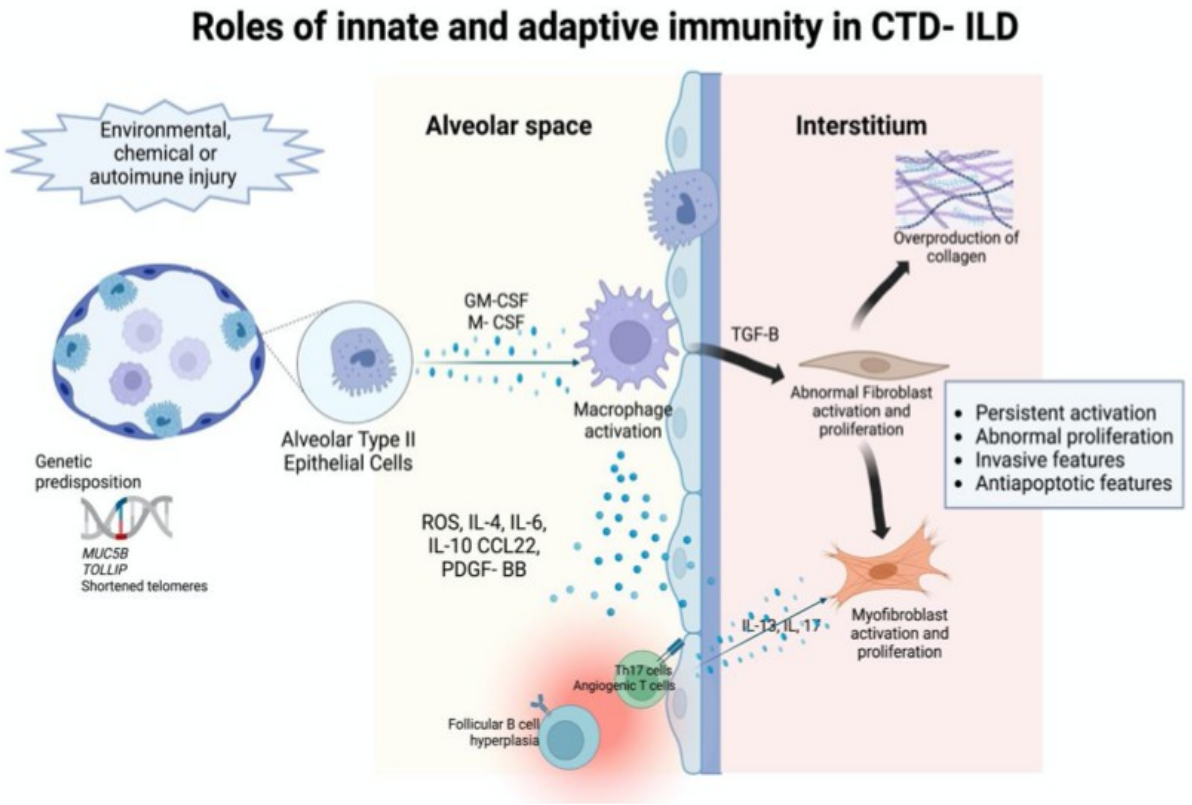
- Immunosuppressor
- Antifibrotic
- Wait and see

What are the objectives?

- Clinical improvement (Dyspnoea, Cough, Quality of life, …)
- Prognosis improvement

Can we be helped by pathophysiology or histopathological features?

Pathophysiology of CTD-ILD



- Abnormal interactions between endothelial cells, mononuclear cells (lymphocytes and monocytes) and fibroblasts

- **Inflammation**
  - T lymphocytes secrete Th2 type cytokines:
    - The most important is IL-4, which stimulate fibroblast proliferation and increase collagen synthesis.
    - IL-13 and IL-4: induce the activation of alternative pro-fibrotic M2 macrophages (produce high levels of TGFβ), PDGF and FGF) favoring myofibroblast activation

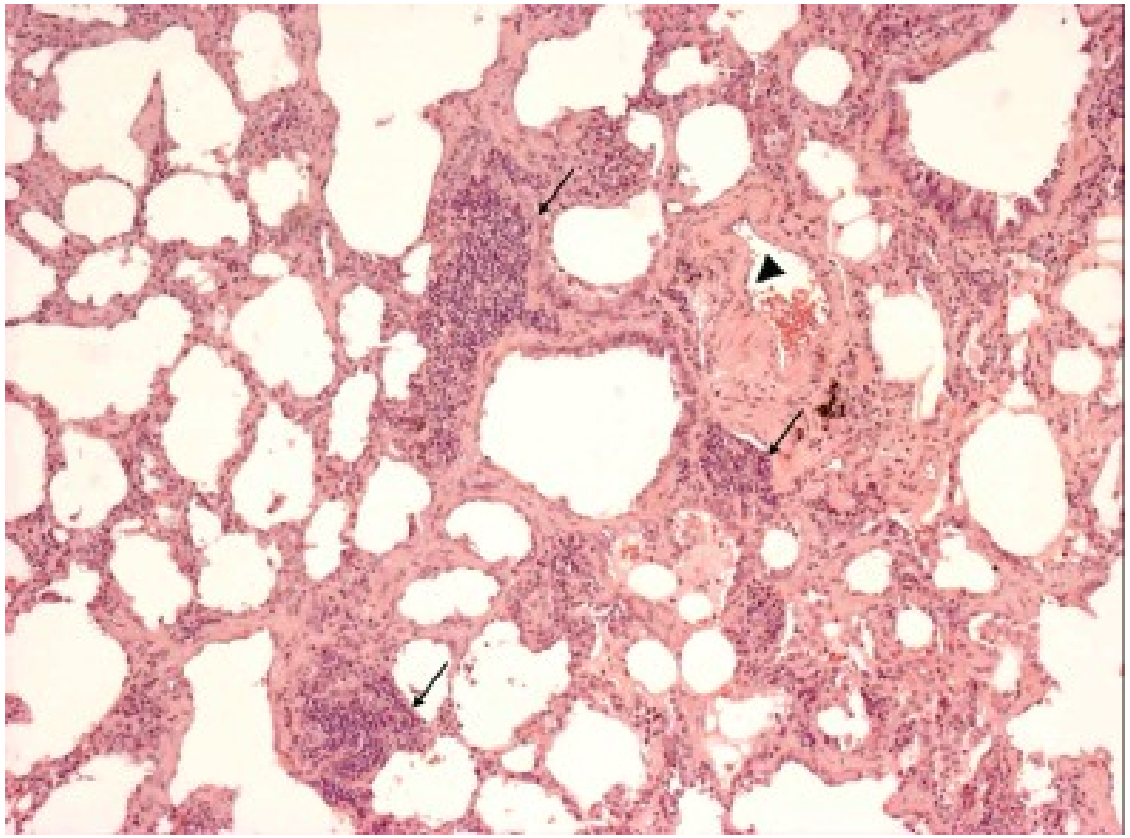
- **Oxidative stress**
  - Monocytes of SSc patients produce larger quantities of superoxide anions than do monocytes of healthy subjects in vitro
  - Activation of fibroblasts and collagen production

Chiang, Int J Mol Sci 2023

Histopathological features of CTD-ILD
UIP subtype

- 272 patients IPF/UIP vs 48 CTD/UIP, patients)
- Surgical lung biopsy
- CTD/UIP compared to IPF/UIP:
  - **More germinal centers**
  - **More total inflammation with plasma cells**
  - **Fewer fibroblastic foci**
  - **Smaller HC spaces.**

(CTD/UIP group:
  - Younger
  - More women and nonsmokers
  - Better survival)



Song, Chest 2009

Can we be helped by reported studies?

- A lot of low-quality retrospectives studies
- Few Randomized Controlled Trials (RCT)

- **On CTD-ILD**

➢**With immunosuppressor**

- SLS I
  Cyclophosphamide (CYC) *vs.* Placebo in **SSc-ILD**
- SLS II
  CYC v*s.* Mycophenolate Mofetyl (MMF) in **SSc-ILD**
- FocuSSced
  Tocilizumab *vs.* Placebo in **SSc**
- RECITAL
  CYC *vs.* Rituximab (RTX) in **CTD-ILD**

➢**With antifibrotic**

- SENSCIS
  Nintedanib *vs.* Placebo in **SSc-ILD**
- TRAIL1
  Pirfenidone *vs*. Placebo in **RA-ILD**

- **On progressive pulmonary fibrosis (PPF) including CTD-ILD**

➢**RCT with antifibrotic**

- INBUILD
  Nintedanib *vs*. Placebo in **progressive pulmonary fibrosis**
- RELIEF
  Pirfenidone *vs*. Placebo in **progressive pulmonary fibrosis**

➢**Series with immunosuppressors**

➢Rescue therapy with RTX

➢Rescue therapy with CYC

SLS I: CYC *vs*. Placebo in SSc-ILD

- Oral CYC (n=73, FVC:68%) *vs*. placebo (n=72, FVC:69%)

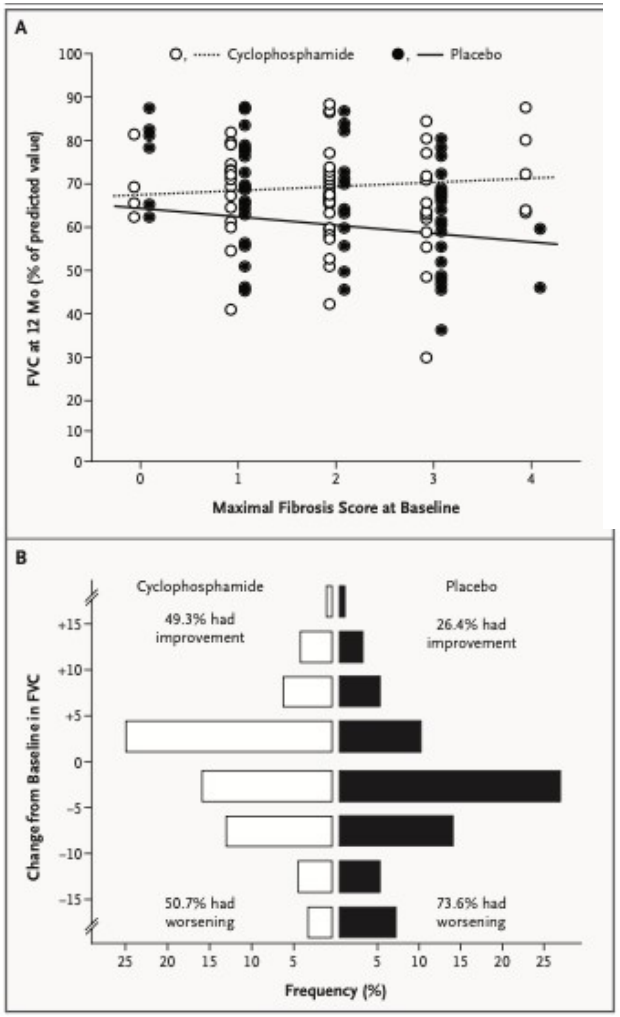
➢mean absolute difference in FVC at 12 months ≃ 2.5 %

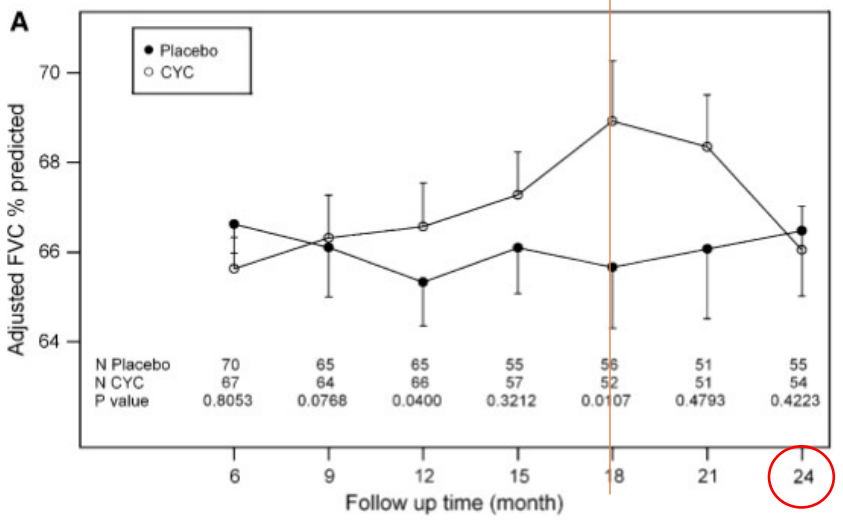
➢49.3 % *vs*. 26.4 % had any improvement in the FVC

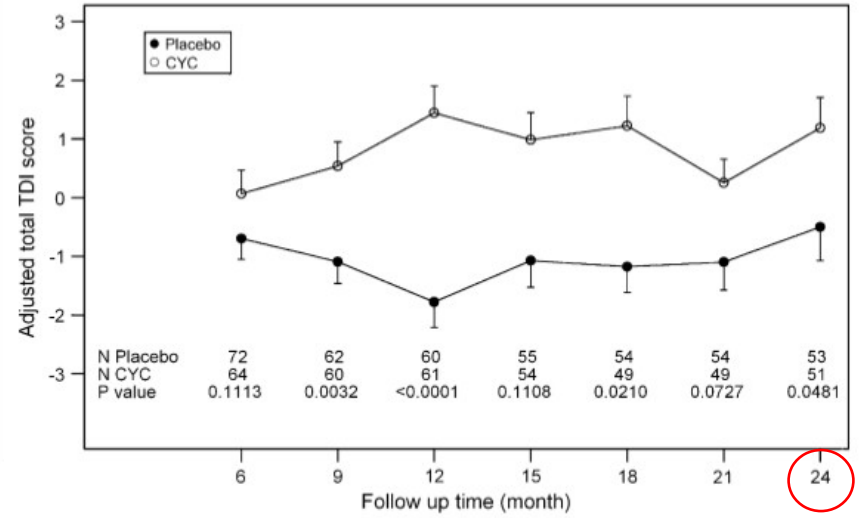
➢**Clinical improvement**

- **Dyspnoea**
- **SF36/HAQ**
- **Cough:**

CYC : 71% → 56% vs. Placebo: 68% → 68%



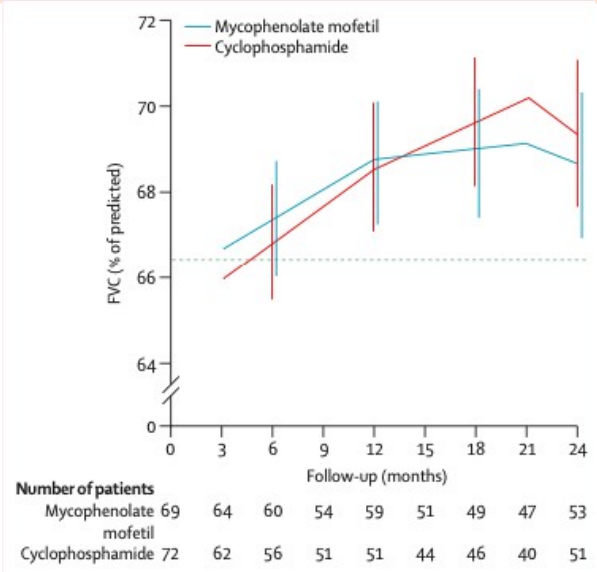


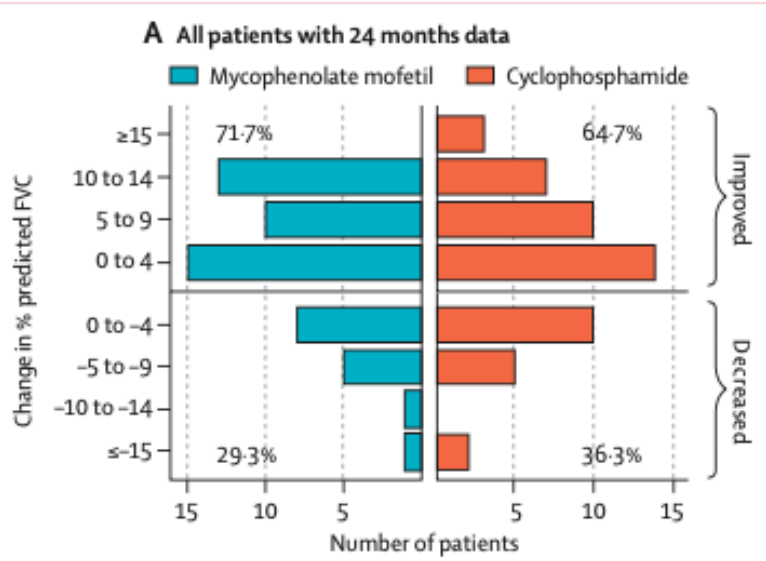


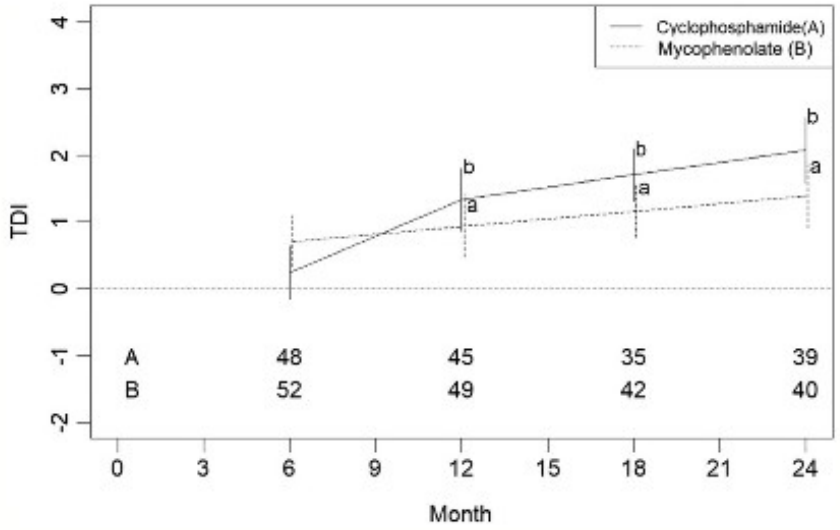
Tashkin, N Eng J Med 2006; Tashkin Am J Respir Crit Care Med 2007

SLS II: CYC *vs*. MMF in SSc-ILD

- Oral CYC (n=73, FVC:66.5%) for 12 months *vs*. MMF (n=69, FVC: 66.5%) for 24 months
- ➢Change of adjusted predicted FVC at 24 months: + 2.88% *vs*. + 2.19% predicted
- ➢64.7 % *vs*. 71.7 % had any improvement in the FVC
- ➢**Clinical improvement**





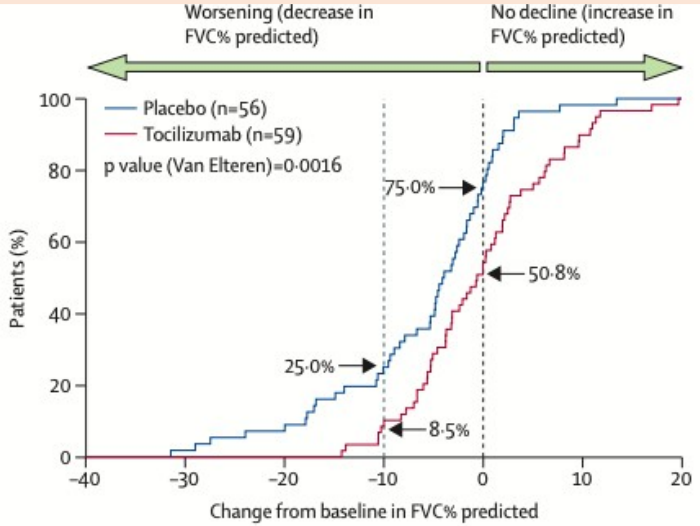


Taskin, Lancet Respir Med 2016; Tashkin, Chest 2016

FocuSSced: Tocilizumab *vs*. Placebo in SSc

- Tocilizumab (n=108, FVC:80.3%) *vs*. Placebo (n=106, FVC: 83.9%) in diffuse SSc, 136 patients with ILD
- **Primary endpoint**: difference in change from baseline to week 48 in mRSS.

➢Not significant

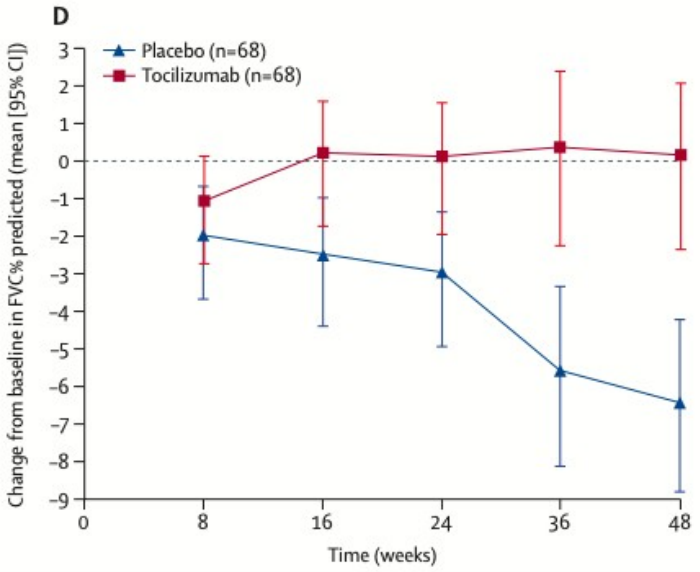


- **Secondary endpoints**: FVC% predicted at week 48

➢Patients with FVC worsening (>10%): 8.5% vs. 25%

➢difference in FVC between tocilizumab (n=68) and placebo (n=68) : 238 mL (6.4%) among participants

➢**No benefit with respect to health-related quality of life (HAQ, SGRQ)**



Khanna, Lancet Respir Med 2020

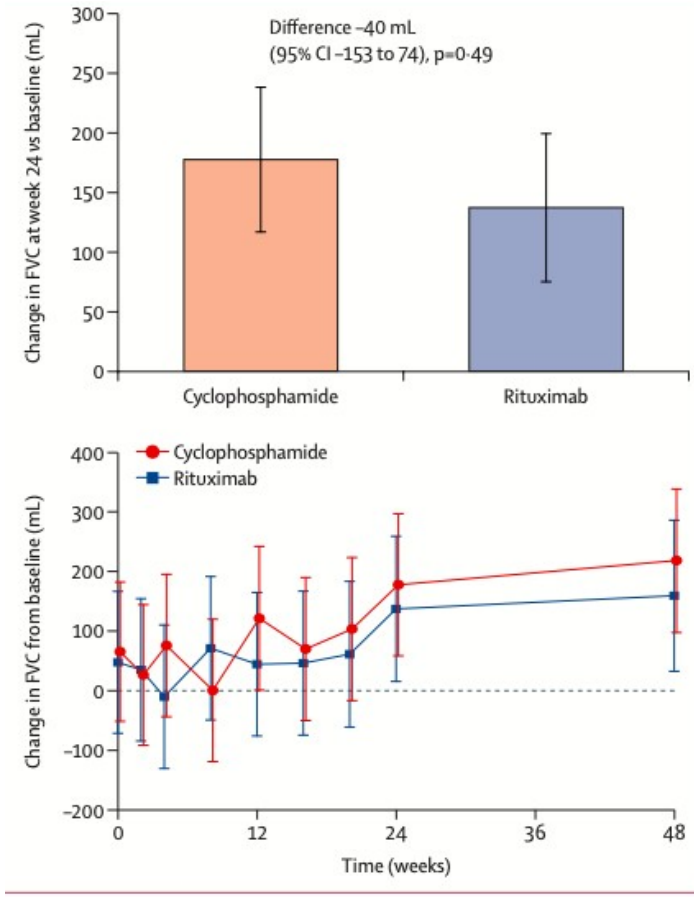
RECITAL: CYC *vs*. RTX in CTD-ILD

- IV RTX (n=49, FVC: 68%) *vs*. IV CYC (n=48, FVC : 71%)
- Severe or progressive CTD-ILD
- SSc (n=37), Myositis (n=44), or MCTD (n=16)

➢ Improvement in FVC (+99mL *vs*. +97mL)

➢ **Quality of life (KBILD/EQ-5D/SGRQ)**:
- Improvement at week 24 and week 48

(More adverse events were reported in the CYC group than in the RTX group)



Maher, Lancet Respir Med 2023

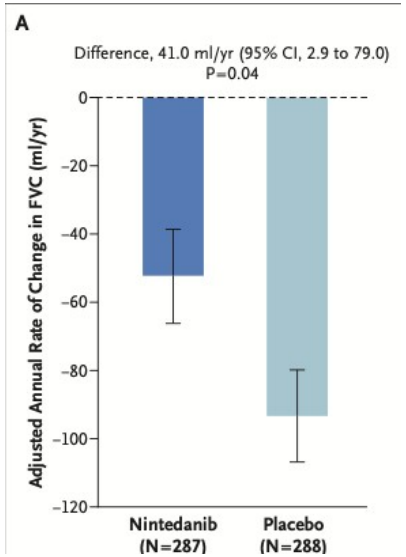
SENSCIS: Nintedanib *vs*. Placebo in SSc-ILD

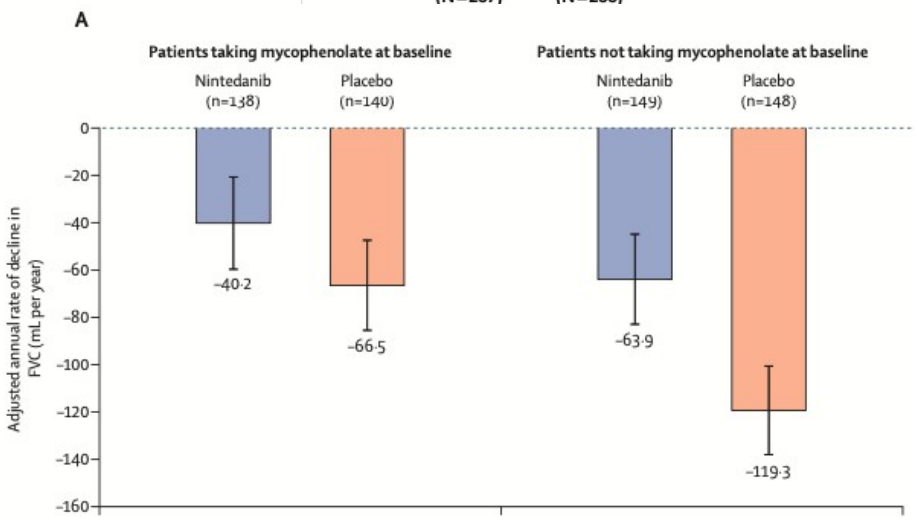
- Nintedanib (n=288, FVC:72.4%) *vs*. Placebo (n=288, FVC: 72.7%

➢ Lower annual rate of change in FVC in the nintedanib group than in the placebo group: -52.4 mL *vs*. -93.3 mL

➢ No heterogeneity in the treatment effect of nintedanib between the subgroups by MMF use

- 48.4% were receiving MMF at baseline.





➢ **No benefit with respect to health-related quality of life**

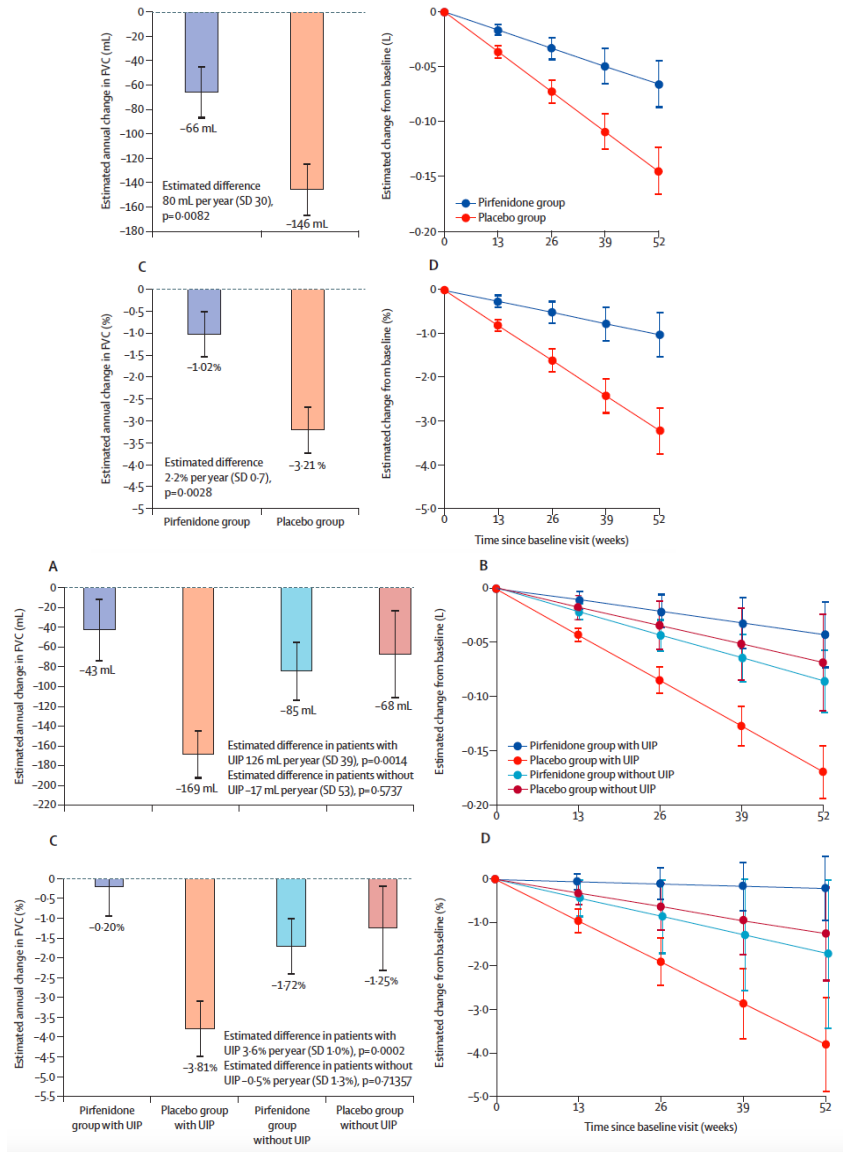
(The percentage of patients who had an **adverse event** that led to the discontinuation of the assigned intervention was higher in the nintedanib-16%- group than in the placebo group-8.7%)

Distler, NEJM 2019; Highland, Lancet Respir Med 2021

TRAIL1: Pirfenidone *vs*. Placebo in RA-ILD

- Pirfenidone (n=63, FVC:69.4%) *vs*. Placebo (n=60, FVC: 70.4%)
- Stopped due to slow recruitment (COVID19)

- Primary End-Point:
  - ➢Decline in FVC% from baseline of 10% or more or death: 11% *vs*. 15% (NS)
- Secondary End Point
  - ➢Slower rate of decline in lung function (annual change)
    - Absolute FVC: –66 mL *vs.* –146 mL; p=0·0082
    - FVC%: –1·02 *vs* –3·21; p=0·0028
  - More pronounced in HRCT UIP pattern
  - **No significant difference in change in Dyspnea-12 scores**



Solomon, Lancet Respir Med 2023

INBUILD: Nintedanib *vs*. Placebo in PPF

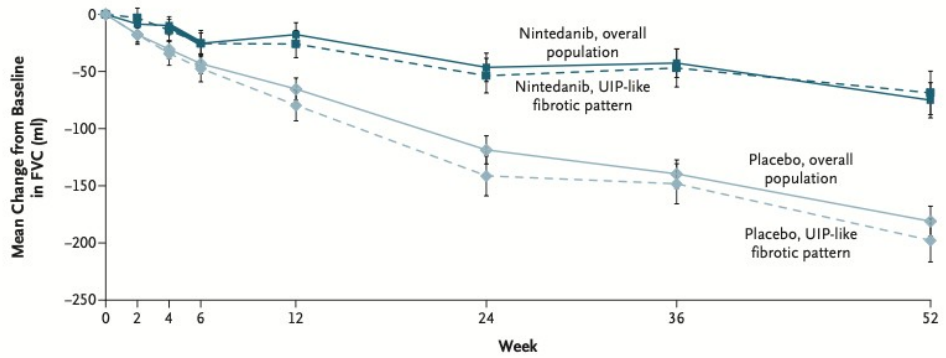
- Nintedanib (n=332, FVC: 68.7%) vs. Placebo (n=331, FVC: 69.3%)
- Progression despite standard treatment

- CTD-ILD (n=170)
  - RA-ILD (89)/SSc-ILD (39)/MCTD-ILD (19)/Other? (22)

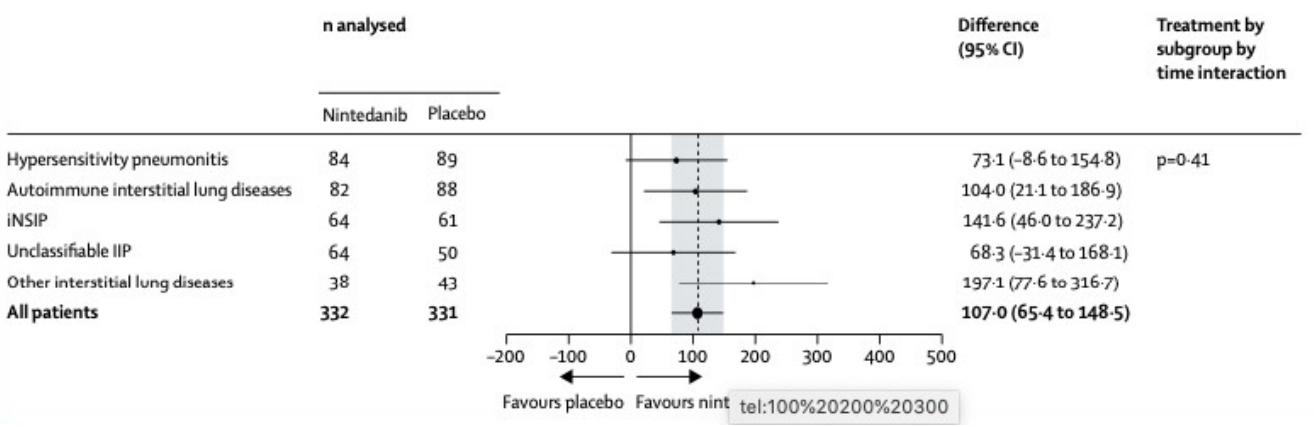
➢Lower decline in FVC (consistent across all the groups)

➢**No significant benefit with respect to health-related quality of life.**

(A greater percentage of patients in the nintedanib group than in the placebo group had **adverse events** leading to a permanent dose reduction (33.1% vs. 4.2%) and to discontinuation of either nintedanib or placebo (19.6% vs. 10.3%)



No. of Patients								
Overall population								
Nintedanib	332	326	320	322	314	298	285	265
Placebo	331	325	326	325	320	311	296	274
Patients with UIP-like fibrotic pattern								
Nintedanib	206	203	200	199	193	180	171	160
Placebo	206	202	202	201	197	190	176	162



Flaherty, N Eng J Med 2019; Wells, Lancet Respir Med 2020

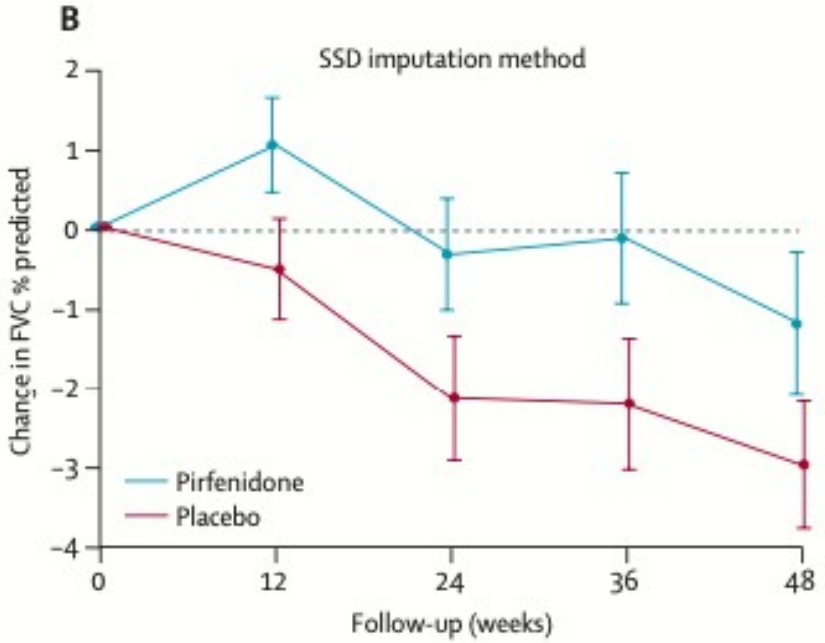
RELIEF: Pirfenidone vs. Placebo in PPF

- Pirfenidone (n=64, FVC:62.6%) vs. Placebo (n=63, FVC:62.2%)
- Stopped due to slow recruitment
- CTD-ILD: n=37
  - 17 RA/8 SSc/5. SS or Myositis/3MCTD/4 overlap

➢Lower decline in FVC

➢the result was similar when the model was stratified by diagnostic group (p=0·042)

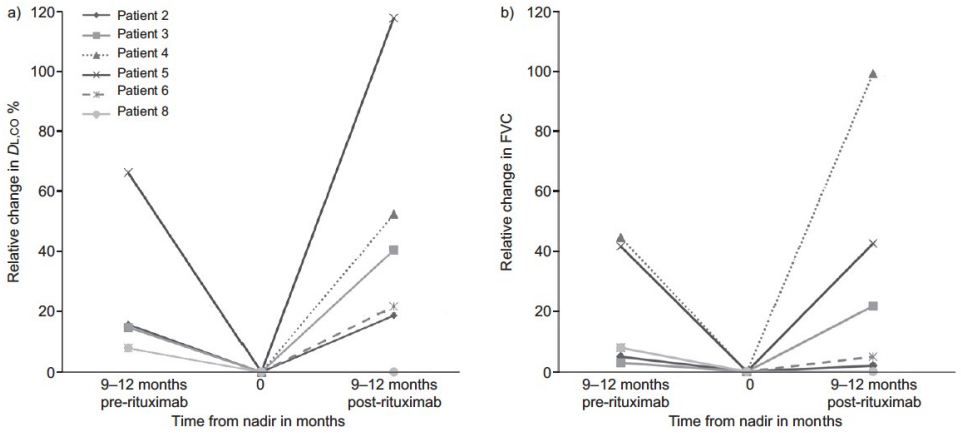
➢**No between-group differences for quality of life, assessed using the SGRQ.**



Behr, Lancet Respir Med 2021

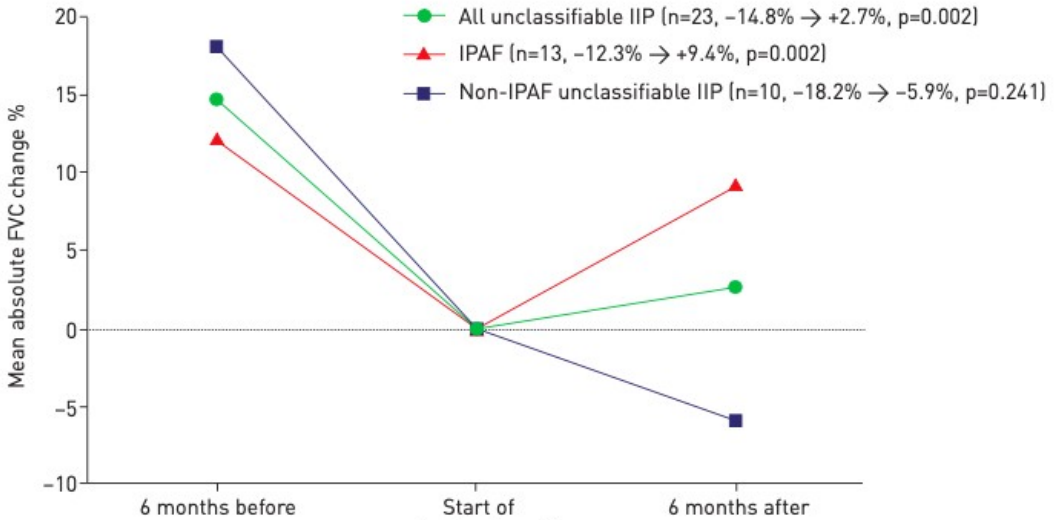
Rescue Therapy in progressive CTD-ILD

RTX



Demographics	Total (n = 43)	Responders (n = 19)	Non-responders (n = 24)	P-value
CTD diagnosis, n				
Primary SS	11 (25.5)	8 (42.1)	3 (12.5)	0.13
IIM	9 (20.9)	5 (26.3)	4 (16.6)	
RA	10 (23.2)	3 (15.7)	7 (29.1)	
MCTD	4 (9.3)	2 (10.5)	2 (8.3)	
SSc	4 (9.3)	0	4 (16.6)	
SLE	2 (4.6)	0	2 (8.3)	
IPAF	3 (6.9)	1 (5.2)	2 (8.3)	
Previous treatment, n				
Prednisone	38	16	22	0.46
Methylprednisolone i.v.	14	8	6	0.64
CYC	18	10	8	0.39
MMF	19	7	12	0.49
AZA	13	6	7	0.79
Other[a]	16	7	9	0.86
Duration of ILD before rituximab, mean (s.d.), months	49.5 (39.3)	34.8 (29.8)	61 (42.2)	0.02
Physiology, mean (s.d.)				
FVC, % predicted	55.3 (23.1)	49.3 (11.6)	58.3 (24)	0.19
DLCO, % predicted	41.9 (16.5)	37.3 (10.2)	47.5 (18.5)	0.13
HRCT pattern, n (%)				
NSIP	18 (41.8)	10 (52.6)	8 (33.3)	0.13
OP	2 (4.6)	1 (4.1)	1 (5.2)	
NSIP-OP	7 (16.2)	4 (21)	3 (12.5)	
UIP (possible or definite)	9 (20.9)	4 (21)	5 (20.8)	
Unclassifiable	7 (16.2)		7 (29.1)	

CYC



Keir, Eur Respir J 2012; Uzunhan, Rheumatology 2016; Wiertz, Eur Respir J 2018

Achieved goals of treatment regarding these studies

Clinical improvement

- YES
  - SLS I (cough)
  - SLS II
  - RECITAL
- NO
  - FocuSSced
  - SENSCIS
  - INBUILD
  - TRAIL1
  - RELIEF

Prognosis improvement

- No result or significant result on survival rate
- Improvement or stabilisation of PFTs is probably better than slow-down

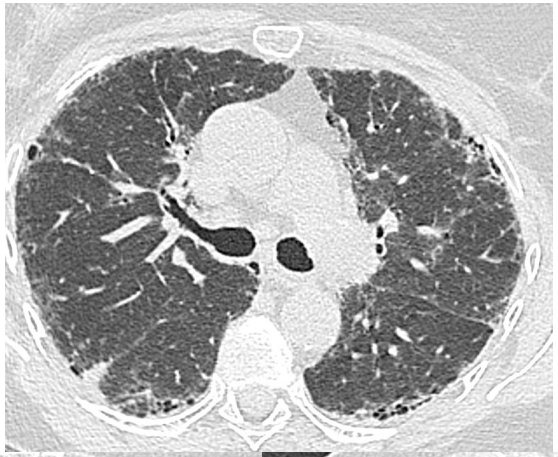
Our patient

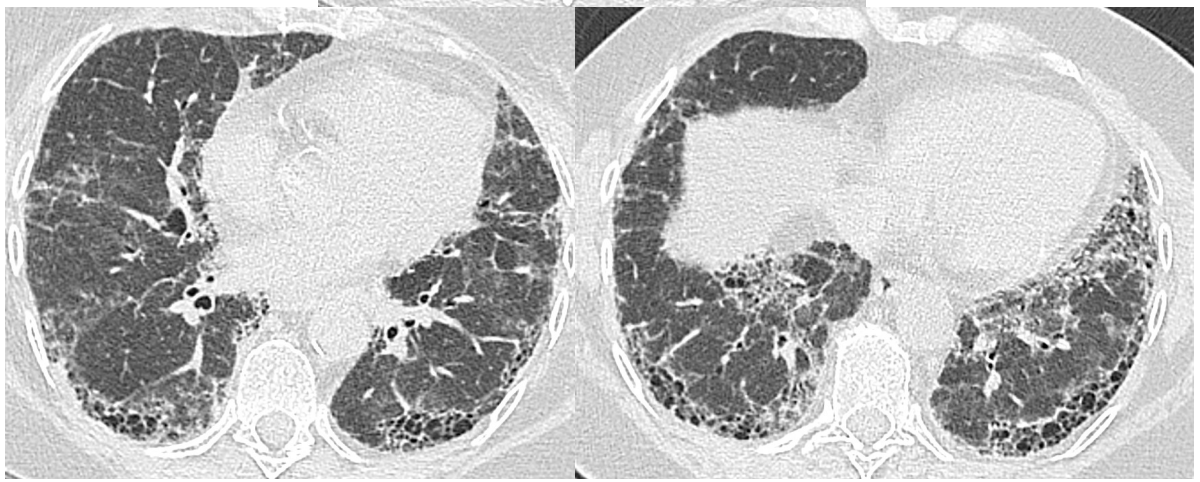
- MDD
  - Worsening is probably secondary to an inflammatory process in the context of Sjogren's Syndrome despite UIP pattern

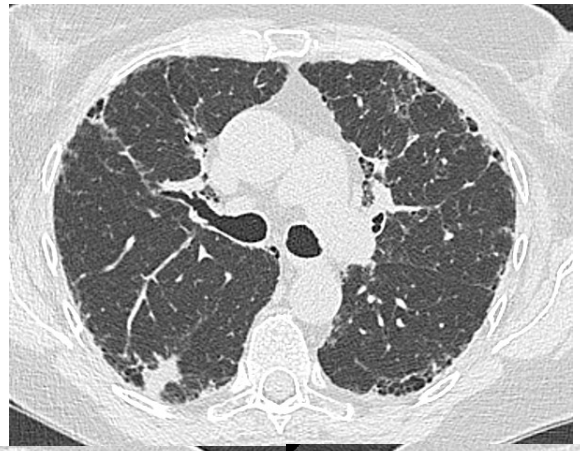
➢Corticosteroids: 0.5 mg/kg and slow tapering until 7.5 mg

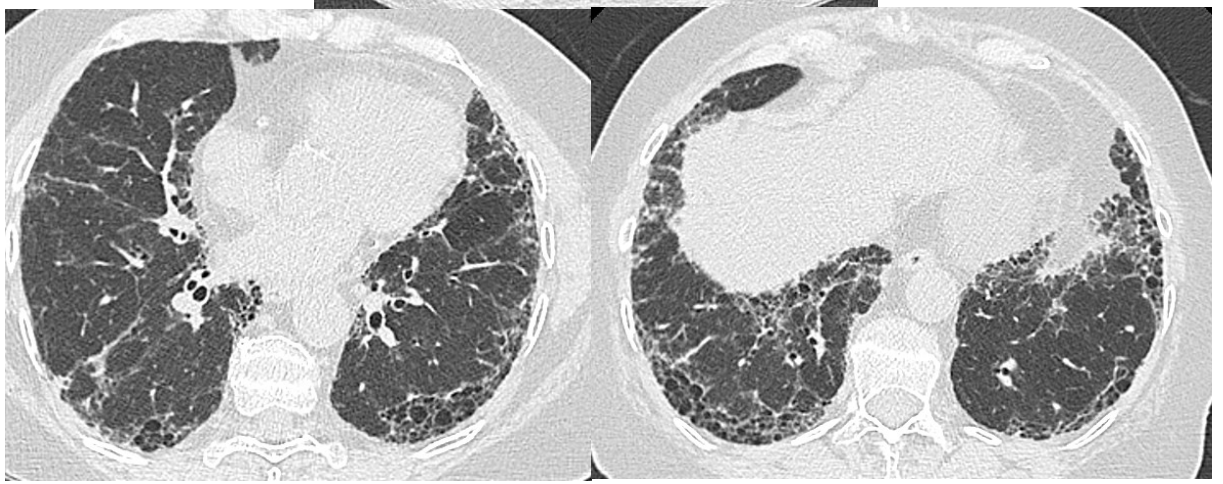
➢Rituximab: D1, D15 (1 g), M6, M12, M18 (500 mg)

	2019	07/2020	12/2020	12/2022
Dyspnoea, mMRC	**1**	**2**	**2**	**1**
FVC, L (%)	2,25 **(75)**	1.82 **(63)**	1,69 **(59)**	**2,04 (74)**
DLCO, %	69	50	ND	**50**









Conclusion

- Dysregulated pathways related to the immunoinflammatory disease leading to lung fibrosis should be a target of therapy on CTD-ILD.
- We should not miss therapeutic window of opportunity to improve clinical status of patients and prognosis of disease.
- The premature use of antifibrotic monotherapy risks loss of the benefits of immunomodulation, applicable to most patients with CTD-ILD.
- Before considering progressive fibrosing CTD-ILD and anti-fibrotic indication, patient should be on conventional appropriate treatment that should probably include rescue immunosuppressor therapy.
- RCTs including immunosuppressors and antifibrotics are the only way to provide an evidence-based answer as to the place of these treatments, sequentially or concomitantly.