Updates in treatment of non-IPF ILD

Dr. Vaibhav Kajaria
SR Pulmonary Medicine
PGIMER Chandigarh

- CTD – ILD

  RA-ILD, SSc-ILD, IIM-ILD, NSIP, IPAF
- PF-ILD
- Hypersensitivity pneumonitis
- Sarcoidosis
- Some investigational therapy

CTD ILD

Rituximab and mycophenolate mofetil combination in patients with interstitial lung disease (EVER-ILD): a double-blind, randomised, placebo-controlled trial

- Multicentre, randomised, double blind, parallel group, placebo-controlled, superiority trial,
- CTD-ILD (40%/32%) or IPAF (27/32%) or IIP (33/37%) and a NSIP pattern
- Rituximab 1gm (n=63) or placebo (n=59) on day 1 and day 15 + mycophenolate mofetil (2 g daily) for 6 months
- Primary: change in percent FVC from baseline to 6 months – LSM change in FVC between-group difference **3.60, (95% CI 0.41–6.80; p=0.0273**)
- Secondary: PFS, better in combination group (crude HR 0.47, **95% CI 0.23–0.96; p=0.03**)

Mankikian J, et al. Eur Respir J. 2023;61(6):2202071

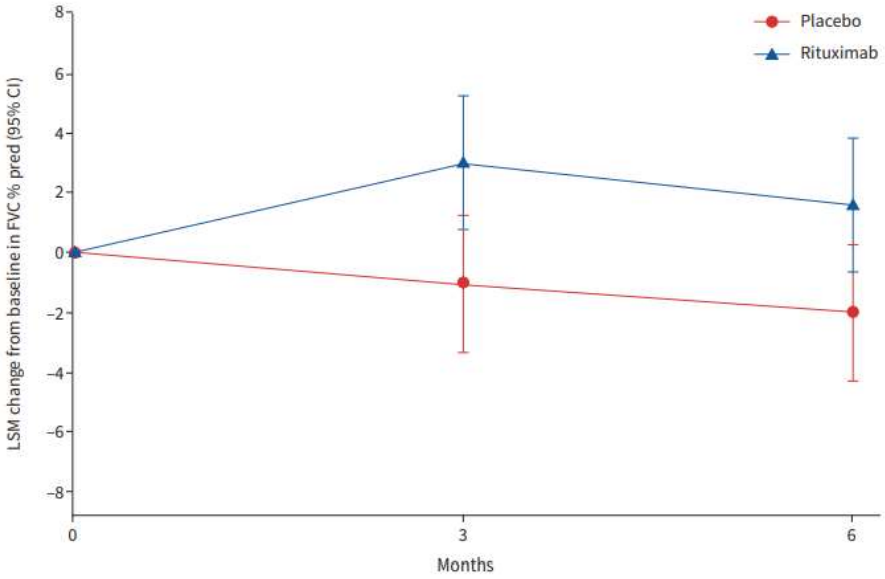
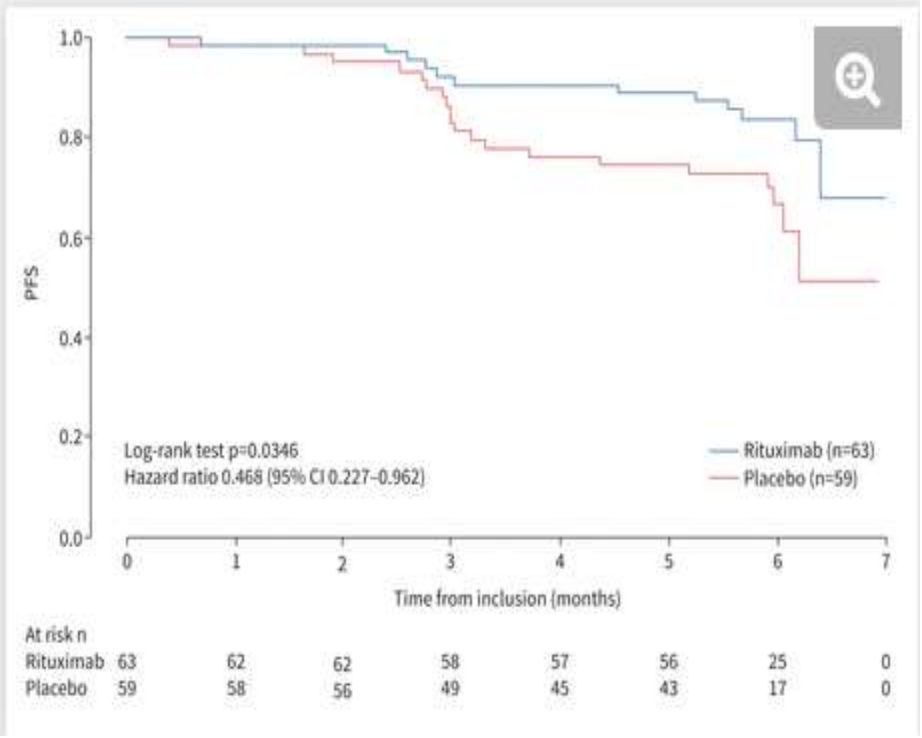
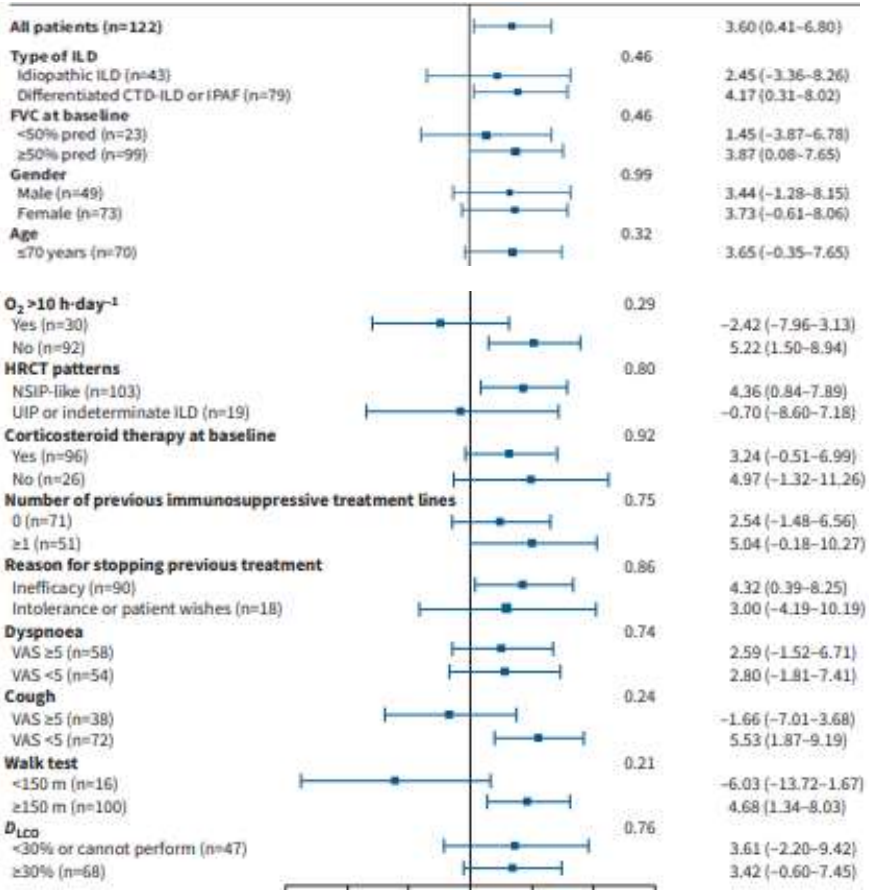


FIGURE 2 Variation from baseline in forced vital capacity (FVC). Shown is the least-squares mean (LSM) change from baseline in FVC (% pred) over the 6-month trial period in the rituximab+mycophenolate mofetil (MMF) group and the placebo+MMF group.

TABLE 2 Primary efficacy end-point

	Rituximab+MMF	Placebo+MMF	Between-group difference (95% CI)	p-value
Participants	63	59		
LSM change in FVC % pred value from baseline to 6 months				
Primary analysis	1.60 (−0.63–3.82)	−2.01 (−4.31–0.29)	3.60 (0.41–6.80)	0.0273
Adjusted model on stratification variables[#]	1.53 (−0.69–3.76)	−2.04 (−4.35–0.26)	3.58 (0.38–6.79)	0.0288


1.0
0.8
0.6
0.4
0.2
0.0
PFS
Log-rank test p=0.0346
Hazard ratio 0.468 (95% CI 0.227–0.962)
Rituximab (n=63)
Placebo (n=59)
0
1
2
3
4
5
6
7
Time from inclusion (months)
At risk n
Rituximab 63 62 62 58 57 56 25 0
Placebo 59 58 56 49 45 43 17 0


All patients (n=122) 3.60 (0.41–6.80)
Type of ILD 0.46
Idiopathic ILD (n=43) 2.45 (−3.36–8.26)
Differentiated CTD-ILD or IPAF (n=79) 4.17 (0.31–8.02)
FVC at baseline 0.46
<50% pred (n=23) 1.45 (−3.87–6.78)
≥50% pred (n=99) 3.87 (0.08–7.65)
Gender 0.99
Male (n=49) 3.44 (−1.28–8.15)
Female (n=73) 3.73 (−0.61–8.06)
Age 0.32
≤70 years (n=70) 3.65 (−0.35–7.65)
O_2 >10 h·day^{-1} 0.29
Yes (n=30) −2.42 (−7.96–3.13)
No (n=92) 5.22 (1.50–8.94)
HRCT patterns 0.80
NSIP-like (n=103) 4.36 (0.84–7.89)
UIP or indeterminate ILD (n=19) −0.70 (−8.60–7.18)
Corticosteroid therapy at baseline 0.92
Yes (n=96) 3.24 (−0.51–6.99)
No (n=26) 4.97 (−1.32–11.26)
Number of previous immunosuppressive treatment lines 0.75
0 (n=71) 2.54 (−1.48–6.56)
≥1 (n=51) 5.04 (−0.18–10.27)
Reason for stopping previous treatment 0.86
Inefficacy (n=90) 4.32 (0.39–8.25)
Intolerance or patient wishes (n=18) 3.00 (−4.19–10.19)
Dyspnoea 0.74
VAS ≥5 (n=58) 2.59 (−1.52–6.71)
VAS <5 (n=54) 2.80 (−1.81–7.41)
Cough 0.24
VAS ≥5 (n=38) −1.66 (−7.01–3.68)
VAS <5 (n=72) 5.53 (1.87–9.19)
Walk test 0.21
<150 m (n=16) −6.03 (−13.72–1.67)
≥150 m (n=100) 4.68 (1.34–8.03)
D_{LCO} 0.76
<30% or cannot perform (n=47) 3.61 (−2.20–9.42)
≥30% (n=68) 3.42 (−0.60–7.45)

Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial

- ILD related to SSCILD (40%), IIM (45%), or mixed CTD (15%)- FVC -70% DLCO -40%
- RTX n=49 (1gm at weeks 0 and 2 iv) or CYC n= 48 (600 mg/m^2 BSA every 4 weeks iv for six doses)
- Similar efficacy in FVC improvement difference, -40 mL (95% CI -153 to 74; p=0.49)
- Fewer adverse events in RTX vs. CYC group. GI & nervous system, general and infusion site reactions more common in CYC arm
- Total steroid exposure reduced in Ritiuximab arm : mean dose per patient was 42·9 mg/day of in the cyclophosphamide cohort and 37·6 mg/day hydrocortisone in the rituximab group, equivalent to a 12·3% reduction
- Terminated early due to COVID 19 pandemic (n=97 vs 104 targeted)

Maher TM et al.,. Lancet Respir Med. 2023 Jan;11(1):45-54.

	Cyclophosphamide group		Rituximab group		Adjusted difference (95% CI)	p value
	n	Change from baseline	n	Change from baseline		
FVC, mL						
24 weeks	45	99 (329)	43	97 (234)	-40 (-153 to 74)	0·493
48 weeks	42	138 (440)	35	112 (249)	-58 (-178 to 62)	0·345
DL_{CO}, mL/min per kPa						
24 weeks	44	0·058 (0·706)	38	0·264 (0·573)	0·186 (-0·054 to 0·425)	0·425
48 weeks	38	0·131 (1·080)	32	0·288 (0·612)	0·117 (-0·137 to 0·372)	0·372
6 min walk distance, m						
24 weeks	46	10·4 (78·6)	40	10·9 (74·2)	-0·72 (-24·76 to 23·32)	0·953
48 weeks	39	15·1 (82·8)	32	-6·8 (69·8)	-22·46 (-48·43 to 3·51)	0·090
EQ-5D score						
24 weeks	43	3·5 (20·5)	41	6·2 (17·7)	3·06 (-3·05 to 9·18)	0·326
48 weeks	40	-1·2 (23·5)	35	3·9 (15·8)	4·77 (-1·73 to 11·27)	0·150
GDA score						
24 weeks	37	-2·9 (2·1)	35	-2·8 (1·8)	-0·14 (-0·85 to 0·57)	0·700
48 weeks	33	-2·9 (2·5)	26	-1·7 (2·3)	0·90 (0·11 to 1·68)	0·025
KBILD score						
24 weeks	45	9·4 (20·8)	42	8·8 (17·0)	0·40 (-5·73 to 6·52)	0·899
48 weeks	43	5·6 (25·6)	35	6·4 (16·2)	1·15 (-5·34 to 7·64)	0·728
SGRQ score						
24 weeks	42	-4·8 (19·6)	39	-3·4 (15·4)	0·63 (-5·64 to 6·91)	0·843
48 weeks	40	-6·4 (24·3)	35	-3·2 (16·6)	2·82 (-3·69 to 9·34)	0·396

	Cyclophosphamide group (n=50)	Rituximab group (n=51)
All events	646	445
Blood and lymphatic system disorders	3 (<1%)	0
Cardiac disorders	10 (2%)	6 (1%)
Ear and labyrinth disorders	2 (<1%)	1 (<1%)
Eye disorders	16 (2%)	9 (2%)
Gastrointestinal disorders	170 (26%)	71 (16%)
General disorders and administration site conditions	91 (14%)	52 (12%)
Hepatobiliary disorders	1 (<1%)	1 (<1%)
Immune system disorders	0	2 (<1%)
Infections and infestations	50 (8%)	46 (10%)
Injury, poisoning, and procedural complications	8 (1%)	5 (1%)
Investigations	11 (2%)	8 (2%)
Metabolism and nutrition disorders	5 (1%)	3 (1%)
Musculoskeletal and connective tissue disorders	44 (7%)	40 (9%)
Nervous system disorders	72 (11%)	35 (8%)
Psychiatric disorders	9 (1%)	10 (2%)
Renal and urinary disorders	8 (1%)	1 (<1%)
Reproductive system and breast disorders	5 (1%)	4 (1%)
Respiratory, thoracic, and mediastinal disorders	94 (15%)	101 (23%)
Skin and subcutaneous tissue disorders	38 (6%)	32 (7%)
Surgical and medical procedures	1 (<1%)	0
Vascular disorders	7 (1%)	16 (4%)

Data are number of events (% of total events reported per cohort).

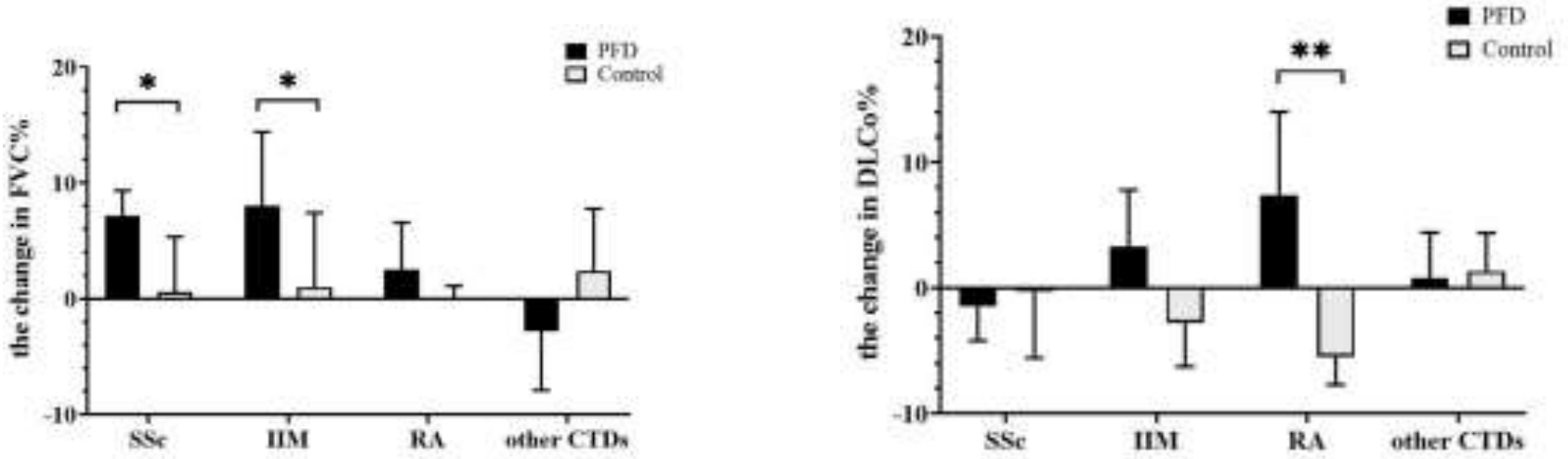
***Table 3*: Adverse events by system, organ, and class, reported to week 48 for all randomised participants**

The Efficacy and Safety of Pirfenidone Combined With Immunosuppressant Therapy in Connective Tissue Disease-Associated Interstitial Lung Disease: A 24-Week Prospective Controlled Cohort Study

- 111 patients with CTD ILD, background IS therapy +/- pirfenidone (n=56 vs n=55).
- SSC ILD (30) , RA (17) , IIM (51) , other CTD (13)
- FVC was 85-90% , majority NSIP except in RA group
- Response to pirfenidone was different in different CTD ILD
- Patients with SSc and IIM showed obvious improvements in FVC%, especially patients with SSc-UIP and IIM-non-UIP
- In RA, the subsets of patients with non-UIP and a lower baseline DLCO% most benefited from PFD.

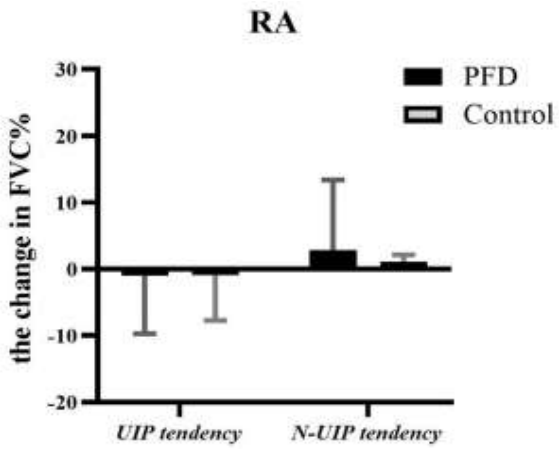
Wang J etal., Front Med (Lausanne). 2022 May 12;9:871861.

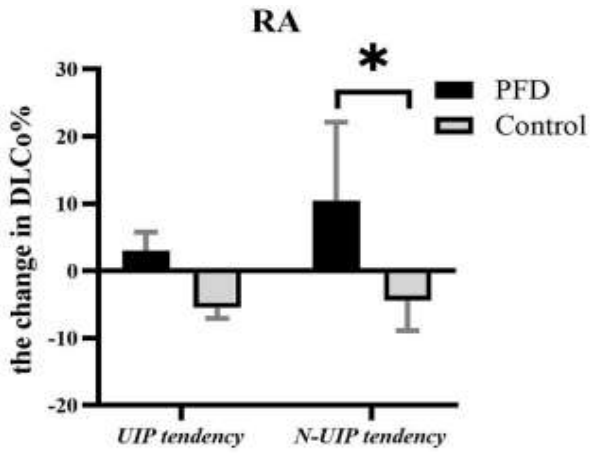
	SSc (n = 30)	IIM (n = 51)	RA (n = 17)	Other CTDs (n = 13)
Age-years	45.17 ± 12.96	50.75 ± 10.57	56.12 ± 11.87	53.23 ± 10.73
Females (%)	29 (97.0)	39 (76.0)	13 (76.0)	12 (92.0)
BMI (kg/m^2)	23.16 ± 3.77	23.93 ± 2.92	25.36 ± 3.10	23.23 ± 3.34
Former smoker (%)	4 (13.0)	4 (8.0)	3 (18.0)	1 (8.0)
Disease course (months)	24.00 (11.25–55.75)	7.50 (1.00–17.00)	60.00 (4.50–95.50)	31.00 (1.75–111.00)
FVC%	90.97 ± 21.17	84.8 ± 18.19	87.43 ± 16.16	87.08 ± 20.00
DLCo%	65.55 ± 18.34	68.71 ± 14.4	66.89 ± 12.17	54.58 ± 15.25
FVC%<70%	4 (13.3)	15 (29.4)	2 (11.8)	2 (15.4)
DLCo%<70%	16 (57.1)	28 (56.0)	10 (58.8)	12 (92.3)
Activity-related dyspnea (%)	21 (70.0)	33 (65.0)	9 (53.0)	6 (46.0)
Unusual physical signs (%)	8 (27.0)	14 (27.0)	4 (24.0)	3 (23.0)
Thoracic HRCT scan (%)				
UIP	3 (10.0)	6 (12.0)	7 (44.0)	1 (8.0)
NSIP	27 (90.0)	42 (82.0)	7 (44.0)	12 (92.0)
OP	0 (0.0)	3 (6.0)	1 (6.0)	0 (0.0)
LIP	0 (0.0)	0 (0.0)	1 (6.0)	0 (0.0)
UIP tendency on HRCT (%)	11 (36.7)	17 (33.3)	9 (52.9)	4 (30.8)
ESR (mm/h)	35.50 (17.75–55.75)	18.00 (8.25–35.75)	50.00 (29.50–86.50)	28.50 (9.25–48.25)
CRP (mg/L)	0.80 (0.37–2.72)	0.62 (0.22–5.10)	6.49 (3.40–18.00)	1.46 (0.54–2.72)
Hemoglobin (g/L)	127.50 (116.50–137.75)	135.50 (127.30–146.00)	134.00 (117.00–142.00)	132.50 (117.00–143.50)
Albumin (g/L)	46.05 (42.48–48.10)	43.30 (38.08–45.98)	41.60 (37.60–44.85)	44.45 (42.43–48.18)
Globulin (g/L)	30.85 (28.75–33.63)	26.00 (22.75–30.85)	30.30 (25.75–33.20)	29.70 (25.20–37.35)
Baseline treatment				
GC use (%)	27 (90.0)	51 (100.0)	16 (94.1)	12 (92.3)
GC dosage (mg/d prednisone)	10.00 (5.00–15.00)	20.0 (12.5–45.00)	12.50 (7.50–20.00)	7.50 (2.80–20.00)
HCQ use (%)	25 (83.3)	36 (70.6)	12 (70.6)	10 (76.9)
Present DMARDs (%)				
None	3 (10.0)	6 (11.8)	1 (5.9)	2 (15.4)
MMF	16 (53.3)	12 (23.5)	0 (0.0)	7 (53.8)
TAC	1 (3.3)	24 (47.1)	8 (41.7)	1 (7.7)
JAKi	9 (30.0)	6 (11.8)	4 (23.5)	0 (0.0)
Others	1 (3.3)	3 (5.9)	4 (23.5)	3 (23.1)
Previous treatment				
GC use (%)	27 (90.0)	51 (100.0)	15 (88.2)	12 (92.3)
HCQ use (%)	23 (76.7)	36 (70.6)	11 (64.7)	11 (84.6)
DMARDs use (%)	25 (86.2)	45 (88.2)	15 (88.2)	12 (92.3)



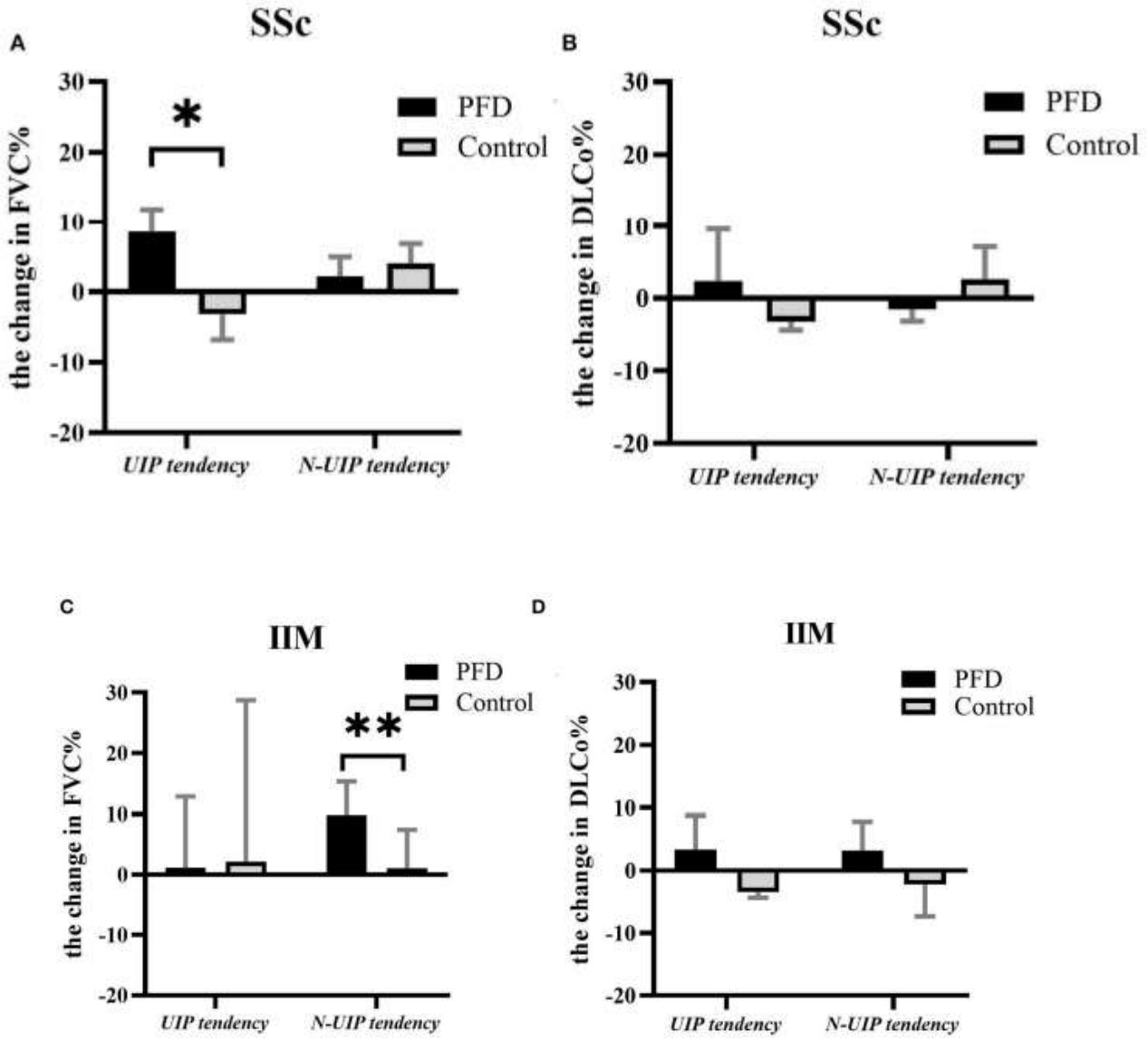
- After 24 weeks improvement in FVC% in the SSc-PFD 6.60% (3.10–8.46%), vs 0.55% (−6.80 to 5.35%) in the SSc-no-PFD group (p = 0.042).
- IIM: PFD vs no PFD : 7.50% (0.55–14.45%) vs. 1.00% (−4.65 to 7.43%) (p = 0.016)
- DLCo% of RA-PFD improved by 7.40% (2.18–14.00%) vs RA-no-PFD decrease of 5.50% (−7.70 to −1.00%) from baseline (p = 0.002)

Item	Category	Total			SSc-ILD			IIM-ILD			RA-ILD		
	Baseline PFT	Pirfenidone	Control	*p*	Pirfenidone	Control	*p*	Pirfenidone	Control	*p*	Pirfenidone	Control	*p*
Change in FVC%	FVC% ≥ 70%	4.10 (−1.40 to 7.85)	0.30 (−3.10 to 4.68)	**0.050***	6.60 (1.23 to 11.50)	0.10 (−6.80 to 4.60)	**0.047***	6.30 (0.50 to 10.50)	1.10 (−3.30 to 6.80)	0.089	0.00 (−5.98 to 4.85)	0.00 (−2.80 to 1.10)	0.643
	(*n*)	40	48		11	15		15	21		8	7	
	FVC% ≥ 70%	10.88 (0.80 to 17.30)	1.00 (−7.20 to 14.20)	0.300	8.46 (3.80 to 8.54)	14.2 (-)	0.180	15.10 (0.35 to 19.10)	0.90 (−10.70 to 22.60)	0.221	9.85 (1.00 to 18.70)	-	-
	(*n*)	16	7		3	1		10	5		2	0	
Change in DLCo%	DLCo% ≥ 70%	−3.50 (−7.00 to 4.60)	−3.80 (−6.40 to 3.30)	0.969	−4.20 (−5.00 to 3.00)	−3.80 (−5.45 to 8.73)	0.519	−4.20 (−11.30 to 2.30)	−3.80 (−10.30 to 1.30)	0.815	6.25 (−3.75 to 18.95)	−5.00 (−6.40 to −2.50)	0.157
	(*n*)	16	27		3	10		9	13		4	3	
	DLCo% ≥ 70%	4.40 (−1.80 to 8.45)	−0.50 (−5.50 to 5.53)	0.057	−0.40 (−3.25 to 8.45)	3.65 (−6.28 to 5.60)	0.723	6.40 (−2.80 to 12.50)	0.70 (−4.70 to 10.20)	0.333	7.40 (2.18 to 14.03)	−6.60 (−8.60 to 2.13)	**0.011***
	(*n*)	38	28		10	6		15	13		6	4	





Non UIP tendency
DLCO% 10.40 vs. −4.45%



UIP tendency
FVC% (8.05 vs -3.20%)

Non UIP tendency
FVC% 10.50 vs. 1.00%

- Immunosupressants have been used to manage CTD related ILD
- Cyclophophamide has been the most commonly used steroid sparing medication
- Rituximab has been tried in some studies along with immunosuppressant and has shown benefit in patients with CTD ILD and NSIP pattern (EVER-ILD)
- Rituximab has also shown similar efficacy to cyclophosphamide with favourable side effect profile (RECITAL)
- In a small study of japanese patients rituximab (n=9) has shown better results than cyclophosphamide(n=30)
- Rituximab is an emerging drug and holds promising results which ***may*** eventually make it as a preferred agent rather than cyclophosphamide
- Pirfenidone may be beneficial in small subset of patients of CTD ILD depending on their phenotype, needs more investigation

A retrospective study of the efficacy of JAK inhibitors or abatacept on rheumatoid arthritis-interstitial lung disease

Marika Tardella[1] · Marco Di Carlo[1] · Marina Carotti[2] · Luca Ceccarelli[3] · Andrea Giovagnoni[2]

- Retrospective analysis of JAK inhibitors vs Abatacept in RA-ILD
- 1st to compare the effect on JAKi vs conventional therapy abatacept in RA **ILD**
- RA-ILD JAKi therapy TFN (n=13) PO 5 mg BID or baricitinib (n=18) PO 4 mg daily or Abatacept (n=44) 125 mg/ week s/c for at least 18 months
- FVC 81.7% and DLCo 59.2%
- Results : HRCT fibrosis changes : worsened" (progression of 15% or more), "stable" (changes within 15%) or "improved" (reduction of 15% or more)
- Treatment with JAKis or ABA was related to stability or improvement of RA-ILD in 83.9% and 88.6% of patients, respectively.

Tardella M etal., Inflammopharmacology. 2022 Jun;30(3):705-712. doi: 10.1007/s10787-022-00936-w

	JAKis	Abatacept
antiCCP	16 (51%)	23 (52.3%)
RF	19 (61%)	28 (63.6%)
Prednisolone	21 (67%)3.3mg/day	31 (70%), 3.7mg/day
Deteriorated HRCT	5 (11%)	5 (16%)
Stable HRCT	32 (72%)	20 (65%)
Improved HRCT	7 (16%)	6 (19%)

Baricitinib and the Risk of Incident Interstitial Lung Disease: A Descriptive Clinical Case Report from Clinical Trials

3770 patients with RA from 8 RCT (4 phase 3, 3 phase 2, 1 phase 1b) 12,358 patient-years of exposure (PYE).

Baricitinib:

> *In total, across eight studies and 3770 patients, there were 21 cases of non-infectious ILD, with an EAIR of 0.17 per 100 PYE. Six were reported as serious and 15 as non-serious resulting in an incidence rate of 0.05 per 100 PYE and 0.12 per 100 PYE*

This value is comparable with Tofacitinib , :

> *Tofacitinib, also an oral Janus kinase inhibitor, reported a similar incidence rate of 0.18 per 100 PYE for non-infectious chronic ILD at both doses of 5 mg and 10 mg daily*

Salvarani C,etal.,. Rheumatol Ther. 2021 Sep;8(3):1435-1441

Safety, tolerability, and efficacy of pirfenidone in patients with rheumatoid arthritis-associated interstitial lung disease: a randomised, double-blind, placebo-controlled, phase 2 study

- TRAIL1 : randomized, double-blind, placebo-controlled, trial done in 34 centers
- 63 [51%] in the pirfenidone group and 60 [49%] in the placebo group
- Stopped early : slow recruitment and the COVID-19 pandemic
- Primary endpoint: decline in FVC% from baseline of 10% or more or death

  seven [11%] in pirfenidone group *vs* nine [15%] in placebo group; OR 0·67 [95% CI 0·22 to 2·03]; p=0·48 → **not significant**
- Decline in FVC% ≥ 10% (five [8%] in the pirfenidone group vs seven [12%] in the placebo group; OR 0·52 [95% CI 0·14-1·90]; p=0·32) → **not significant**
- Pirfenidone slowed decline in FVC ml (–66 *vs* –146; p=0·0082) and FVC% (–1·02 *vs* –3·21; p=0·0028) → **significant**

Solomon JJ etal., Lancet Respir Med. 2023 Jan;11(1):87-96. doi: 10.1016/S2213-2600(22)00260-0

- Rheumatoid arthritis ILD has been treated with steroids, MMF , rituximab and methotrexate when immunosuppressant's are indicated.
- Recent experience has started favouring JAKi and TNFalpha inhibitors for systemic illness and nintedanib for fibrotic ILD
- Methotrexate has been known to cause *interstitial lung changes per se (0.3-11.6%)**
- JAK inhibitors have a good safety profile with very low incidence rate of ILD
- Abatacept has equal efficacy to JAKi
- Pirfenidone may have a established role eventually -> requires more studies

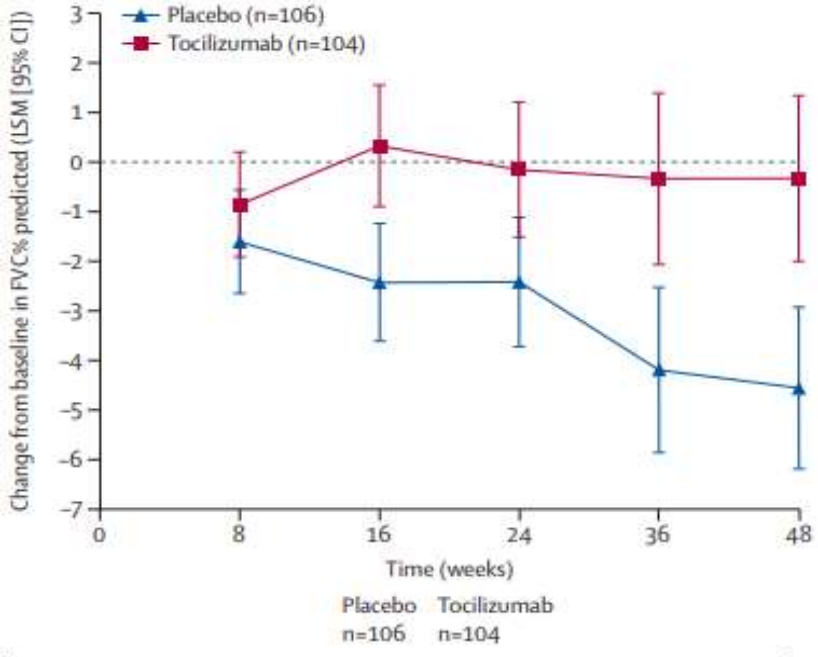
Fragoulis GE, etal.,Front Med (Lausanne). 2019 Oct 23;6:238.

Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial

Dinesh Khanna, MD • Celia J F Lin, MD • Daniel E Furst, MD • Jonathan Goldin, MD • Grace Kim, PhD •

- foCUSSed: Subcut tocilizumab 162 mg or placebo wkly for 48 weeks, stratified by IL-6
- Tocilizumab = 104, Placebo = 106 , FVC – 80%, DLCO – 75-80%
- Primary endpoint: Difference in change from baseline to week 48 in mRSS
- Secondary: FVC% predicted at week 48, time to treatment failure & others
- Change from baseline in FVC% at week 48 favoured Tocilizumab (van Elteren nominal p=0·002 vs placebo) difference in LSM of 4·2 (95% CI 2·0-6·4; nominal p=0·0002)
- Infections : 52% in Toci vs 50% in placebo, SAE : 13 in Toci vs 18 in placebo
- Primary skin fibrosis endpoint was not met, tocilizumab might preserve lung function in people with early SSc-ILD , (50% study population anti topoisomerase 1 positive)
- Rescue immunomodulating therapy : 21% in placebo vs 9% in tocilizumab group

Khanna Detal., Lancet Respir Med. 2020 Oct;8(10):963-974.



	Intention-to-treat population			
	Placebo group (n=106)	Tocilizumab group (n=104)	Difference between treatment groups†	p value
FVC% predicted change from baseline				
Median (95% CI)	−3·9 (−4·8 to −1·6); n=91	−0·6 (−2·4 to 0·9); n=93	3·3 (0·9–4·8)	Nominal p=0·002
LSM (95% CI)	−4·6; n=104	−0·4; n=104	4·2 (2·0–6·4)	Nominal p=0·0002‡
FVC% predicted ≥10% decline	15/91 (17%)	5/93 (5%)	NA§	..
Improvement in FVC% predicted (increase ≥0%)	26/91 (29%)	43/93 (46%)	NA§	..
Absolute change from baseline in FVC, mL				
Week 24, LSM (95% CI)	−101; n=104	−13; n=104	88 (24–152)	Nominal p=0·008‡
Week 48, LSM (95% CI)	−190; n=104	−24; n=104	167 (83–250)	Nominal p=0·0001‡

	Placebo group (n=106)	Tocilizumab group (n=104)	Difference between treatment groups*	p value†
mRSS				
LSM change in mRSS from baseline to week 48	−4·4 (−6·0 to −2·9)	−6·1 (−7·7 to −4·6)	−1·7 (−3·8 to 0·3)	p=0·10‡
LSM change in mRSS from baseline to week 24	−3·1 (−4·3 to −1·8)	−3·7 (−5·0 to −2·4)	−0·6 (−2·3 to 1·0)	Nominal p=0·455
Improvement in mRSS from baseline ≥20%	53 (50%); (40·0–60·0)	75 (72%); (63·0–81·2)	21·9 (9·2–34·6)	Nominal p=0·0007§
Improvement in mRSS from baseline ≥40%	40 (38%); (28·0–47·4)	44 (42%); (32·3–52·3)	4·3 (−8·7 to 17·3)	Nominal p=0·51§
Improvement in mRSS from baseline ≥60%	24 (23%); (14·2–31·1)	18 (17%); (9·6–25·1)	−5·4 (−16·2 to 5·4)	Nominal p=0·33§
Components of treatment failure¶				
Treatment failure	37 (35%)	23 (22%)	HR 0·6 (0·4–1·1)	Nominal p=0·08‖
>10% decrease in FVC% predicted	25 (24%)	13 (13%)	HR 0·55 (0·3–1·1)	Nominal p=0·08‖
mRSS increase >20% and ≥5 points	16 (15%)	10 (10%)	HR 0·64 (0·3–1·4)	Nominal p=0·26‖
SSc-related complication	7 (7%)	5 (5%)	HR 0·79 (0·3–2·5)	Nominal p=0·68‖
Deaths	3 (3%)	1 (1%)	HR 0·37 (0·0–3·6)	Nominal p=0·39‖
Treatment failure excluding decline in FVC% predicted	20 (19%)	13 (13%)	HR 0·67 (0·3–1·4)	Nominal p=0·26‖
Treatment failure excluding increase in mRSS	29 (27%)	17 (16%)	HR 0·62 (0·3–1·1)	Nominal p=0·12‖
Patient-reported and physician-reported outcomes				
HAQ-DI	−0·06 (−0·16 to 0·05); n=102	−0·11 (−0·22 to −0·01); n=103	−0·05 (−0·19 to 0·09)	Nominal p=0·45‡
Patient global assessment VAS	−7·7 (−12·3 to −3·0); n=102	−10·1 (−14·8 to −5·4); n=102	−2·4 (−8·6 to 3·70)	Nominal p=0·43‡
Physician global assessment VAS	−20·0 (−24·8 to −15·22); n=96	−22·5 (−27·3 to −17·6); n=98	−2·5 (−8·7 to 3·8)	Nominal p=0·44‡
FACIT-Fatigue	2·6; n=102	5·1; n=103	2·40 (0·08–4·73)	Nominal p=0·04‡
SHAQ VAS	−0·3 (−0·5 to −0·1)	−0·3 (−0·5 to −0·2)	NA	..
SGRQ	−2·1 (−6·0 to 1·7)	−3·2 (−5·9 to −0·4)	NA	..

Long-Term Safety and Efficacy of Tocilizumab in Early Systemic Sclerosis–Interstitial Lung Disease: Open-Label Extension of a Phase 3 Randomized Controlled Trial

- 82 of 107 in the placebo-tocilizumab group and 85 of 105 in continuous-tocilizumab group completed 96 weeks
- 54 of 89 patients (60.7%) in the placebo-tocilizumab group and 60 of 92 patients (65.2%) in the continuous-tocilizumab group had SSc-ILD at baseline according to HRCT
- *Tocilizumab preserved lung function, slowing decline in FVC, in patients with SSc, including those with ILD*

Khanna D etal., . Am J Respir Crit Care Med. 2022 Mar 15;205(6):674-684.

Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial

- SSc-ILD were randomly assigned (1:1) to receive 150 mg of oral nintedanib (n=288) twice daily or placebo (n=288) for at least 52 weeks
- Primary endpoint: subgroup analysis of rate of decline in FVC over 52 weeks by MMF use at baseline (48% in nintedanib group vs 49% in placebo)
- In patients taking MMF at baseline, the adjusted mean annual rate of decline in FVC was –40·2 mL per year (SE 19·8) with nintedanib and –66·5 mL per year (19·3) with placebo (difference: 26·3 mL per year [95% CI –27·9 to 80·6])
- In patients not taking MMF at baseline, the adjusted mean annual rate of decline in FVC was –63·9 mL per year (SE 19·3) with nintedanib and –119·3 mL per year (19·0) with placebo (difference: 55·4 mL per year [95% CI 2·3 to 108·5])

Highland KB, etal.,Lancet Respir Med. 2021 Jan;9(1):96-106.

- **Post hoc analysis:**

  patients on baseline MMF : absolute decrease in FVC of at least 3·3% (**MCID**) predicted was lower with nintedanib than with placebo (40 [29%] of 138 *vs* 56 [40%] of 140; odds ratio 0·61 [0·37 to 1·01])

  patients not on baseline MMF : (59 [40%] of 149 *vs* 70 [47%] of 148; 0·73 [0·46 to 1·16])

- No heterogeneity in the effect of nintedanib versus placebo on the annual rate of decline in FVC between the subgroups by mycophenolate use (p value for interaction=0·45)

Annual decline

Only placebo	–119·3 mL
Placebo + nintedanib	–63·9 mL
MMF + nintedanib	–40·2 mL
MMF + placebo	–66·5 mL

	Patients taking mycophenolate at baseline				Patients not taking mycophenolate at baseline				p value for interaction
	Nintedanib (n=139)	Placebo (n=140)	Difference	Odds ratio	Nintedanib (n=149)	Placebo (n=148)	Difference	Odds ratio	
Primary endpoint									
Adjusted annual rate of decline in FVC over 52 weeks, mL per year	−40·2 (19·8)	−66·5 (19·3)	26·3 (−27·9 to 80·6)	..	−63·9 (19·3)	−119·3 (19·0)	55·4 (2·3 to 108·5)	..	0·45*†
Key secondary endpoints									
Adjusted absolute change from baseline in mRSS at week 52	−2·4 (0·4)	−2·5 (0·4)	0·04 (−1·01 to 1·09)	..	−1·9 (0·4)	−1·5 (0·4)	−0·44 (−1·47 to 0·58)	..	0·52‡
Adjusted absolute change from baseline in SGRQ total score at week 52	0·7 (1·3)	−0·9 (1·2)	1·6 (−1·9 to 5·0)	..	0·9 (1·2)	−0·9 (1·2)	1·8 (−1·6 to 5·2)	..	0·92‡
Other secondary lung function endpoints									
Adjusted change from baseline in FVC at week 52, mL	−42·2 (20·0)	−78·6 (19·4)	36·43 (−18·3 to 91·2)	..	−66·4 (19·4)	−122·7 (19·1)	56·3 (2·8 to 109·7)	..	0·61‡
Annual rate of decline in FVC % predicted	−0·9 (0·6)	−1·7 (0·5)	0·8 (−0·7 to 2·3)	..	−1·9 (0·5)	−3·4 (0·5)	1·5 (0·1 to 3·0)	..	0·49†
Patients with an absolute decrease from baseline in FVC of >5% predicted at week 52	21/138 (15%)	36/140 (26%)	..	0·52 (0·29 to 0·95)	38/149 (26%)	46/148 (31%)	..	0·76 (0·46 to 1·26)	0·35§
Patients with an absolute decrease from baseline in FVC of >10% predicted at week 52	4/138 (3%)	7/140 (5%)	..	0·57 (0·16 to 1·98)	16/149 (11%)	17/148 (12%)	..	0·93 (0·45 to 1·91)	0·50§

JAK inhibitors and systemic sclerosis: A systematic review of the literature

Clothilde Moriana [a], Thomas Moulinet [a,b], Roland Jaussaud [a], Paul Decker [a,*]

- 69 patients (women 81%) with SSc and treated with JAK inhibitors were identified in 10 publications (four clinical trials and six case reports), FVC 77% of predicted
- 27 (56%) had diffuse SSc, and 21 (43%) had limited SSc, 31 had ILD
- JAKi as 1st line in 35 patients (59%) , tofacitinib (80%), baricitinib in 20%

	Total ($N = 59$) % (n/N) or mean ± SD or median [IQR]	« Naïve » SSc ($N = 35$) % (n/N) or mean ± SD or median [IQR]	Refractory SSc ($N = 24$) % (n/N) or mean ± SD or median [IQR]	p value
FVC at inclusion (% predicted value)	77 [71–81]	76 [71–79.5]	81 [64–91]	0.48
Δ FVC before and after JAKi (% predicted value)	−1 [−4.3–0]	−2 [−4.5–0]	0 [−5–0]	0.57

patients with ILD (n = 31), 28/29 patients (97%) did not experience ILD progression during follow-up time, with an absolute median change of the FVC percentage of predicted value (Δ %FVC) after treatment initiation of − 1 [− 4.3–0]

Moriana C etal., Autoimmun Rev. 2022 Oct;21(10):103168.

- SSc ILD- first line therapy is MMF, corticosteroids high dose are not given for fear of renal crisis, making few other choices available like Cyclophophamide, rituximab , tocilizumab
- Nintedanib as an antifibrotic
- In early ILD options are Tocilizumab and JAKi
- Nintedanib slows progression in ILD alone or in combination with MMF
- Pirfenidone needs evaluation for use alone or in combination with Immunosuppressants

Long-Term Treatment With Azathioprine and Mycophenolate Mofetil for Myositis-Related Interstitial Lung Disease

CHEST

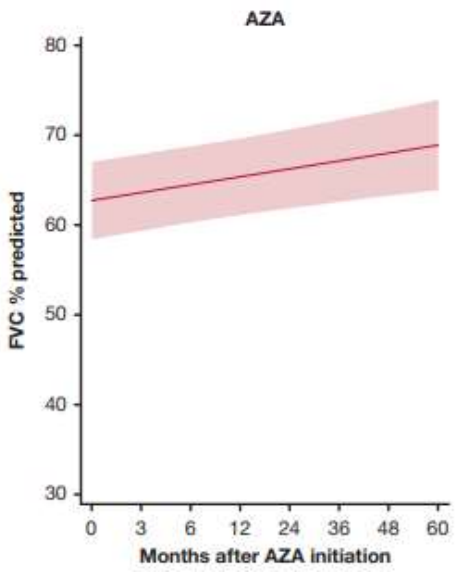
[Original Research **Diffuse Lung Disease**]

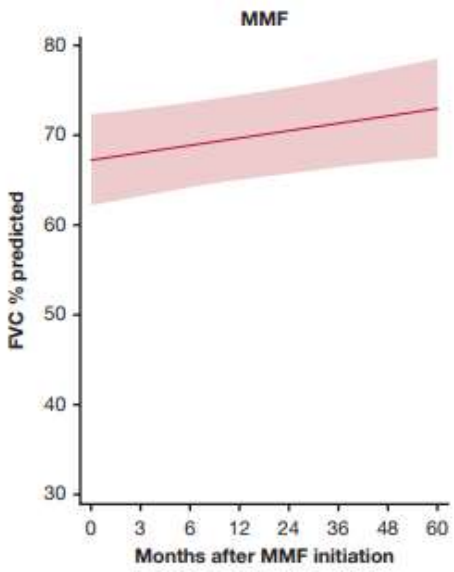
- Retrospective study, patients with Myositis related ILD treated with AZA(n=66) or MMF(n=44) and ***no other steroid-sparing agents were included***

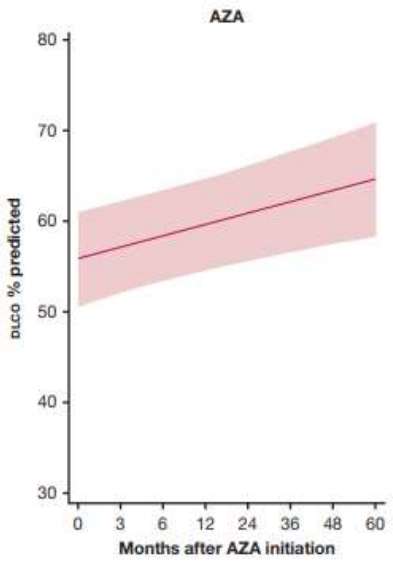
Characteristic	Azathioprine (n = 66)	Mycophenolate Mofetil (n = 44)	*P* Value
DM	40 (60.6)	26 (59.1)	
PM	16 (24.2)	8 (18.2)	
FVC % predicted, mean ± SD	58.4 ± 19.1	72 ± 22.2	.003
TLC % predicted, mean ± SD	58.3 ± 17.8	69.9 ± 19.7	.011
D_{LCO} % predicted, mean ± SD	54.5 ± 21.3	66.6 ± 26.2	.021
Prednisone dose, mean ± SD, mg	28.4 ± 18.7	18.1 ± 12.2	.002

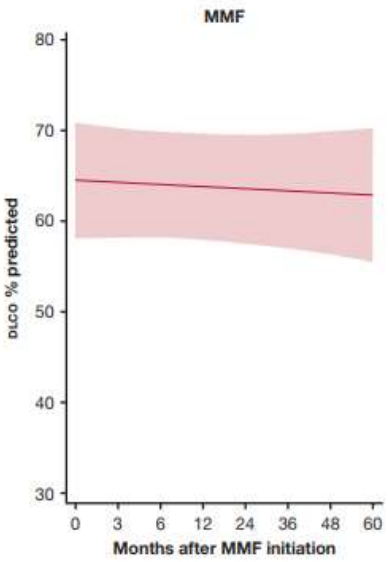
- FVC improvement in both groups, DLCO improved in AZA
- The mean prednisone dose significantly decreased by 15.5 mg at 24 months after AZA initiation (P < .001) and by 6.9 mg after MMF (P < .001)- but very few numbers
- Transaminitis *significantly* more with AZA (15% vs 2%) & discontinuation more with AZA (17 vs 7.5%)

Huapaya JA etal., Chest. 2019 Nov;156(5):896-906







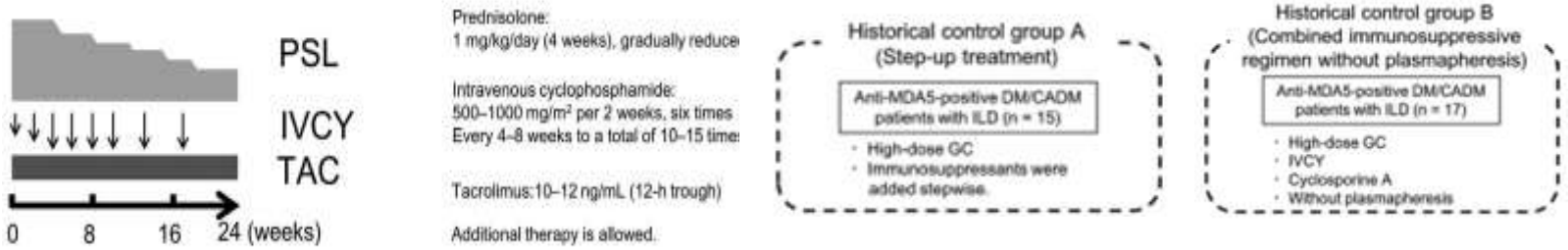


Both therapies significantly improved FVC % predicted at 24 months (AZA, 3.6% [P =0.001]; MMF, 3.3% [P =0.021]

DLCO % predicted, there was a statistically significant improvement for AZA (P =0.002), but not for MMF (P =0.657)

Multicenter Prospective Study of the Efficacy and Safety of Combined Immunosuppressive Therapy With High-Dose Glucocorticoid, Tacrolimus, and Cyclophosphamide in Interstitial Lung Diseases Accompanied by Anti–Melanoma Differentiation–Associated Gene 5–Positive Dermatomyositis

- New-onset anti–MDA-5–positive DM with ILD (n = 29) treated with a regimen of high-dose GCs,tacrolimus & IV CYC +/- plasmapheresis if clinical worsening

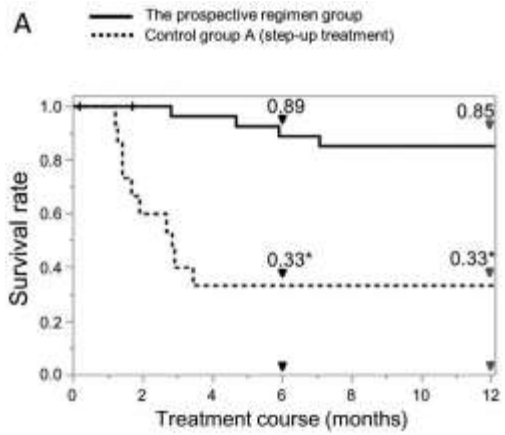


additional group

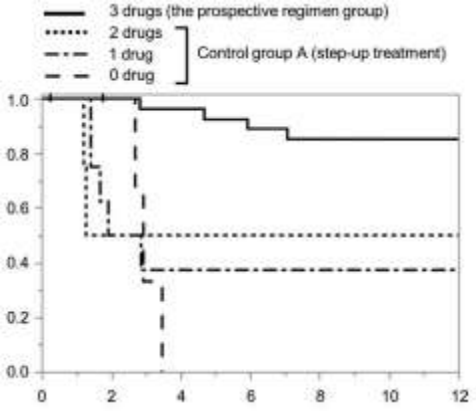
- Primary: 6-month survival combined therapy vs historical control
- Secondary : 12-mnth survival, adverse events, changes in respiratory function,&HRCT
- GCs dose, ivCYC, CNI, plasmapheresis were used less in step up treatment with a longer time gap between institution of therapy

Tsuji H, etal.,. Arthritis Rheumatol. 2020 Mar;72(3):488-498

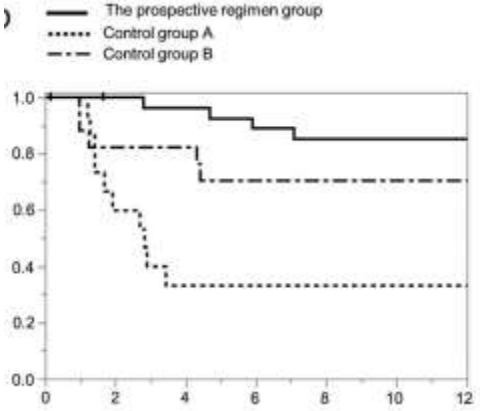
- Combined : 11 hypoxemic, 9 preceived plasmapheresis, out of 11 eight survived
- Survival at 6-months and 12-months in combined group vs step-up treatment group (89% versus 33% and 85% versus 33%, respectively; both P < 0.0001)
- CMV & candida infection, TMP-SMX prophylaxis, hemorrhagic cystitis more in combined group



Survival rates in the prospective regimen group (combined immunosuppressive regimen group) and control group A



Survival rates stratified according to the number of drugs administered within 7 days after hospital admission



Effect of additional treatment with plasmapheresis on survival rates

Intravenous cyclophosphamide improves functional outcomes in interstitial lung disease related to idiopathic inflammatory myopathies

- Iv CYC vs other immunosuppressive regimes as the induction treatment for IIM-ILD
- 47 patients were included: **22 (47%) in the CYC group and 25 (53%) in the non-CYC** group (32% AZA, 28% GC alone, 20% MMF, 16% CNI and MTX and 4% RTX
- Patients in the CYC group received more methyl-prednisolone pulses **(59% vs. 28% in the non-CYC group, p = 0.03)**
- 6- month average dose of prednisone was lower among patients in the CYC group **(11 mg/d vs. 31.1 mg/d in the non-CYC group, p = 0.001)** **????**
- Baseline FVC 66% and DLCO 58%, NSIP pattern CYC vs non CYC (77% vs 44%)

Outcomes according to treatment group.

	Global (n = 47)	CYC (n = 22)	Other IS scheme (n = 25)	p-value
FVC difference from baseline mean (SD)	8.4 (13.5)	11.9 (11.5)	5.6 (14.5)	0.120
FVC improvement/stability/worsening n (%)				
>10% FVC improvement	22 (47%)	14 (64%)	8 (32%)	**0.03**
FVC stability	18 (38%)	8 (36%)	11 (44%)	0.595
>10% FVC worsening	6 (13%)	0	6 (24%)	**0.021**

Moreno-Torres V etal., Semin Arthritis Rheum. 2023 Apr;59:152164. j.semarthrit.2023.152164

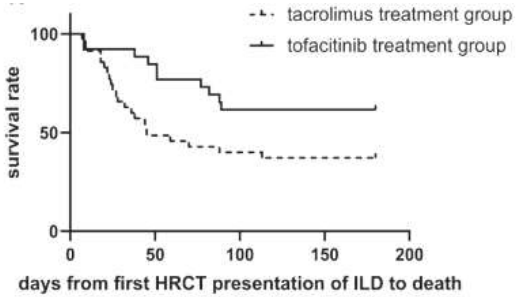
A Retrospective Analysis of Outcome in Melanoma Differentiation–Associated Gene 5–Related Interstitial Lung Disease Treated with Tofacitinib or Tacrolimus

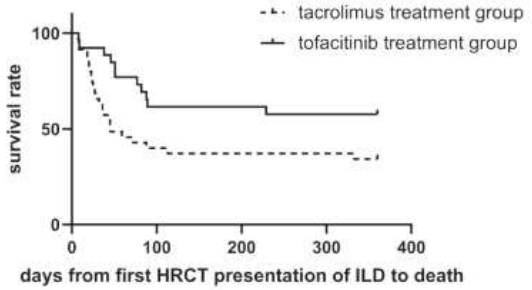
The Journal of Rheumatology

- Tofacitinib (n-26) vs Tacrolimus (n=35) , in MDA-5 related ILD
- Baseline FVC 57-60% and DLCO 55-57%, OP pattern in 60-70%, 1 UIP
- 13 (50.0%) in TOF group and 22 (62.9%) in TAC group were diagnosed with RP-ILD
- Weak anti-MDA5 antibody titre : TOF group (61.5%) vs TAC group (25.7%) P = 0.002.
- Dose: **TOF** 5 mg OD in 2 patients and 5 mg BD in 24 patients, **TAC** – 2-4mg/day
- Other IS therapy were similar & so was the treatment discontinuation rate
- There was no significant difference in the overall incidence of AEs between the 2 groups (TOF group: 19/26, 73.1% and TAC group: 26/35, 74.3%, P > 0.99)

Fan L, etal., J Rheumatol. 2022 Dec;49(12):1356-1364.

- After adjustment for age, sex, smoking history, anti-MDA5 antibody titers, & concurrent use of other steroid-sparing agents, : **TOF exposure was associated with a lower risk of 1-year mortality (hazard ratio [HR] 0.44, 95% CI 0.20-0.96; P = 0.04)**
- The 6-month all-cause mortality of patients with **RP-ILD** in the **TOF group (10/13, 76.9%**) was significantly reduced compared to that in the TAC group **(21/22, 95.5%; P = 0.02)**

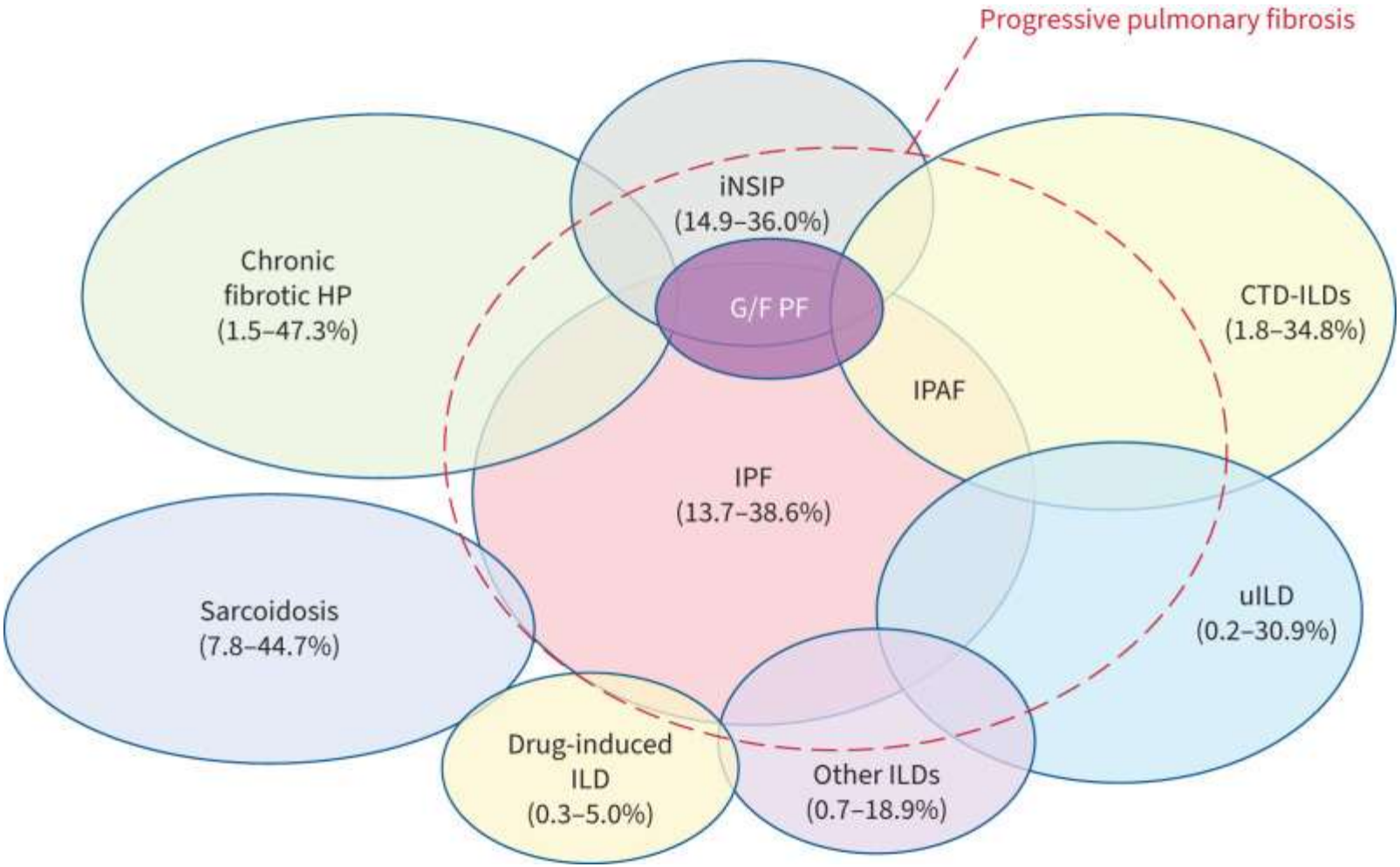




	Tofacitinib Group, n = 13	Tacrolimus Group, n = 22	*P*
Therapy: initial GC dosage, mg/d, median (IQR)	160.00 (40.00-500.00)	160.00 (20.00-500.00)	0.42
Concurrent use of other steroid-sparing agents	8 (61.5)	14 (63.6)	> 0.99
TAC and TOF discontinuation	2 (15.4)	3 (13.6)	> 0.99
6-month mortality	10 (76.9)	21 (95.5)	0.02
1-year mortality	11 (84.6)	22 (100)	0.02

- IIM ILD – 1st line of therapy is steroids
- Adding a 2nd agent is mandatory : cyclophosphamide/ AZA /MMF/ Rituximab
- Cyclophosphamide has been used more commonly and may be better
- Tacrolimus/ciclosporin have also been used
- Tofacitinib may be have better efficacy → needs more analysis/studies
- We know that it's a rapidly fatal disease needing quick institution of therapy often at a higher dose.
- Combined therapy with tacrolimus / iv Cyclophophamide and steroids may be beneficial.
- Plasmapheresis can be used in acute worsening

PF -ILD



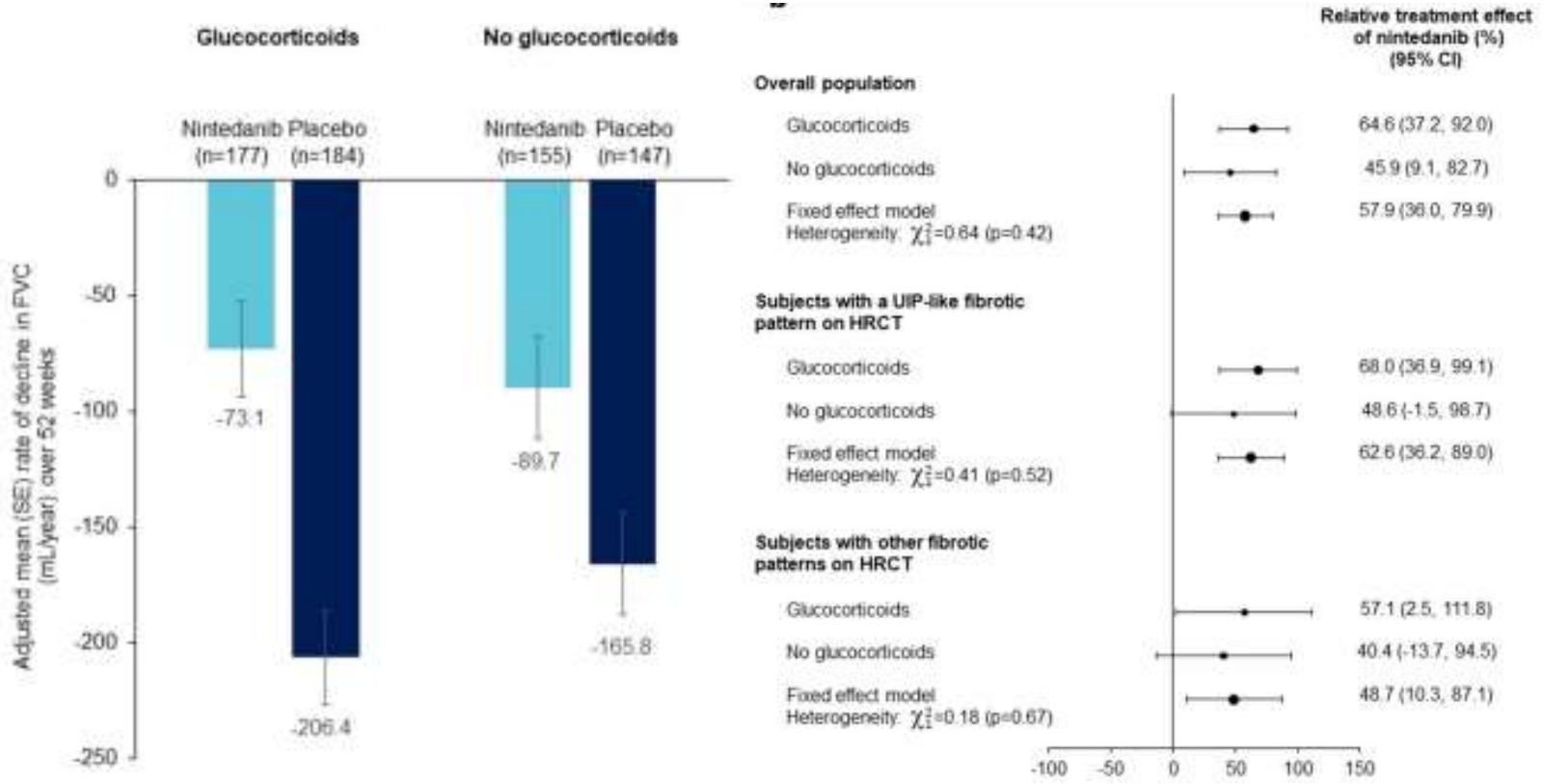
Rajan SK etal.,. Eur Respir J. 2023 Mar 30;61(3):2103187

RESEARCH Open Access

Nintedanib and immunomodulatory therapies in progressive fibrosing interstitial lung diseases

- Investigated the impact of immunomodulatory therapies on the efficacy and safety of nintedanib – post hoc analysis of INBUILD trial
- N=663, predicted FVC 69%, UIP pattern – 63% , 54% on corticosteroids
- Restricted therapies were AZA, cyclosporine, mycophenolate mofetil, CYC, RTX, tacrolimus, *oral glucocorticoids>20 mg/day* or (NAC + steroid +AZA)
- *The interaction P value did not indicate heterogeneity in the treatment effect of nintedanib on reducing the rate of decline in FVC between the subgroups by use versus non-use of glucocorticoids (high-dose or low-dose) at baseline in the overall population (P = 0.18), in subjects with a UIP-like fibrotic pattern on HRCT (P = 0.11) or in subjects with other fibrotic patterns on HRCT (P = 0.80)*

Cottin V etal.,. Respir Res. 2021 Mar 16;22(1):84.



- In progressive fibrosing ILDs other than IPF, the effect of nintedanib on reducing FVC decline was not influenced by the use of immunomodulatory therapies

- Progressive fibrosing ILD encompass ILD of different etiology
- Management is dependent on the primary etiology
- Steroids / Immunomodulatory therapy is started 1st where indicated , eg CTD ILD like RA/SSc ILD, IIM etc.
- Antigen avoidance and corticosteroids in Hypersensitivity penumonitis
- Antifibrotics: in combination to IS therapy sequential or upfront in IPF, RAILD- UIP and SscILD
- Pirfenidone and nintedanib both have been used and the superiority of any one drug has not been established in a head on head trial
- Nintedanib with or without IS has shown good results

Hypersensitivity pneumonitis

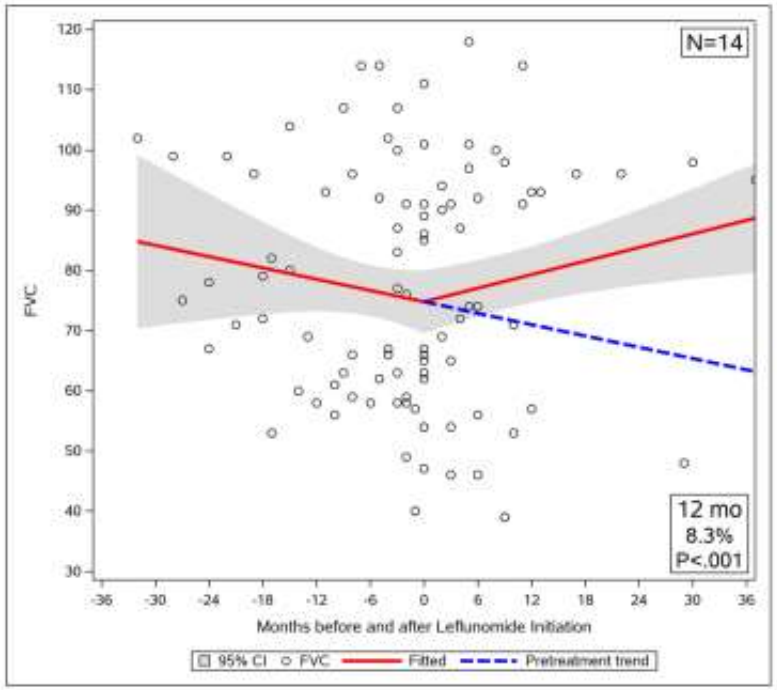
Use of leflunomide in patients with chronic hypersensitivity pneumonitis

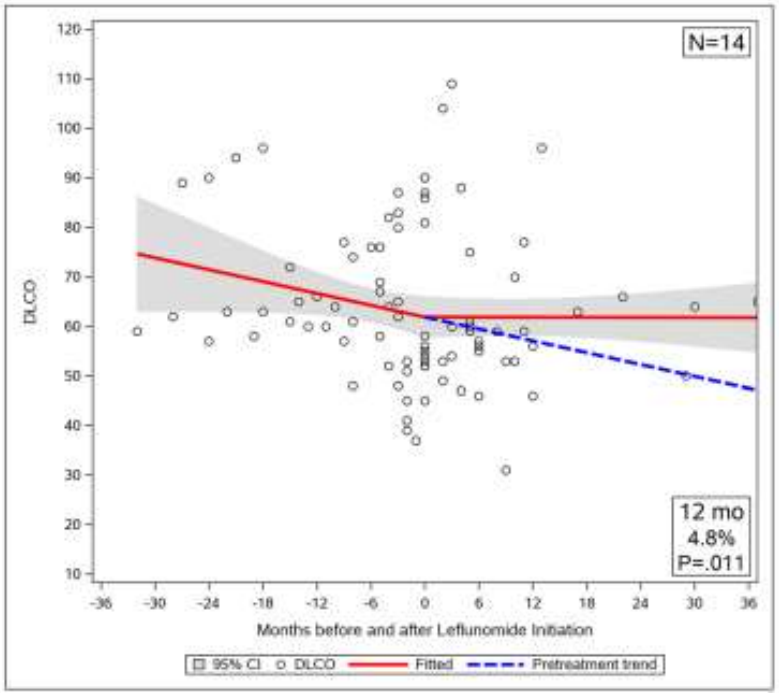
BMC Part of Springer Nature
BMC Pulmonary Medicine

- Retrospective analysis of 28 cHP patients on leflunomide
- 70-80% on corticosteroids at Leflunomide initiation (mean 20mg/day)
- 7 took LEF for 3-6months and 24 took for 6 months or more
- FVC% increased significantly at 1yr(mean **increase 4.4%; 95% CI, 0.7 to 8.5%; *p* = 0.020**) , baseline FVC 66%, and DLCO 51%
- DLCO% predicted did not change significantly after 12 months of LEF treatment (mean increase 0.58% predicted; 95% CI, − 2.7 to 3.9%; *p* = 0.730)
- They also divided patients on the percentage of fibrosis <20% or >20% (n=14 each)
- Leflunomide more beneficial in patients with fibrosis <20%
- **Steroid use decreased : out of 23 , 12 off steroids, 7 on half of initial dose**

Noh S etal., BMC Pulm Med. 2020 Jul 21;20(1):199.

LEF treatment in patients with fibrosis ≤20%

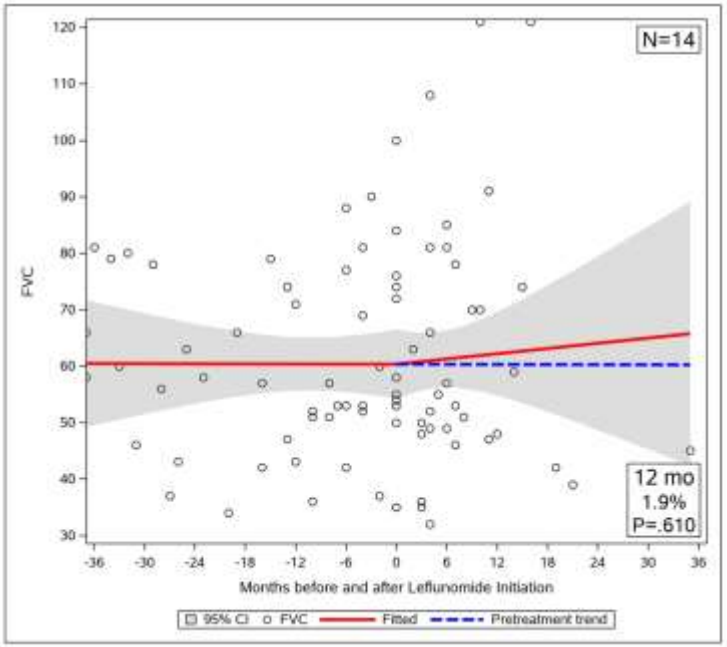


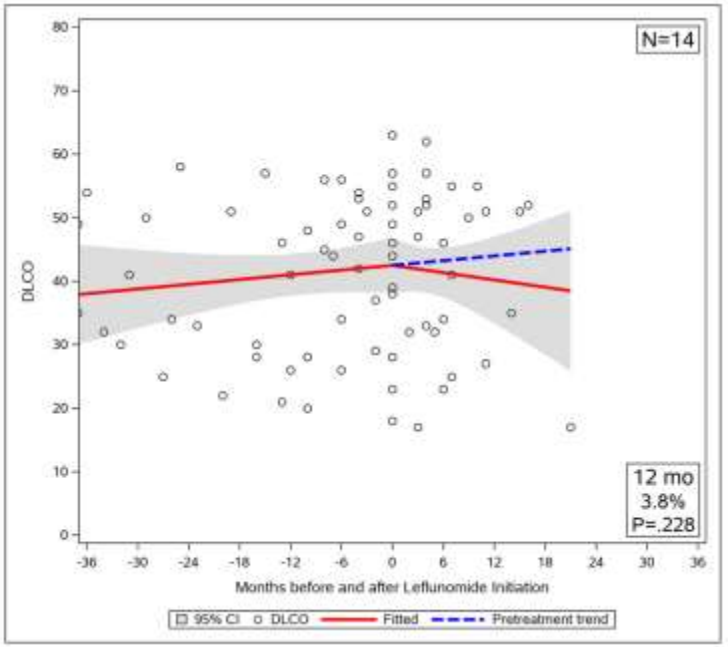


FVC decline of 3.76 ± 3.18% (SEM) predicted/year was reversed to an increase of 4.52 ± 1.67% predicted/year with treatment. **FVC% predicted increased significantly at 12 months (mean increase 8.3% predicted; 95% CI, 3.6 to 13.0%; p < 0.001**

The DLCO slope did not change significantly, from a DLCO of − 4.79 ± 2.57% (SEM) predicted/year to − 0.036 ± 1.31% predicted/year (p = 0.140), but **DLCO% predicted increased significantly at 12 months (mean increase 4.8%predicted; 95% CI, 1.1 to 8.5%; p = 0.011)**

LEF treatment in patients with fibrosis > 20%





FVC decline of 0.037 ± 2.31% (SEM) predicted/year was reversed to an increase of 1.85 ± 4.54% predicted/year with treatment. However, FVC% predicted **did not improve significantly at 12 months (mean increase 1.9%predicted; 95% CI, – 5.5 to 9.3%; p = 0.610)**

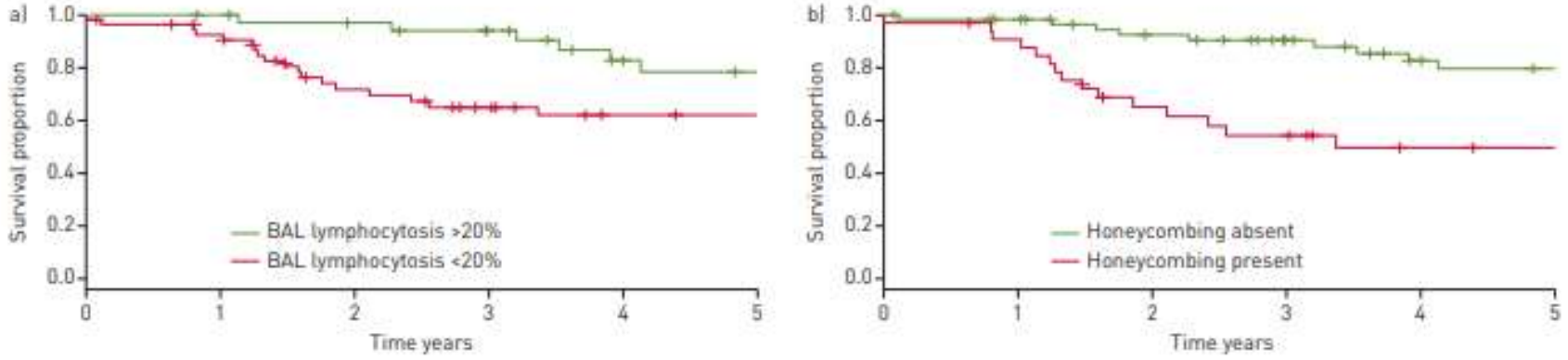
The DLCO slope did not change significantly with treatment (p = 0.456). **DLCO% predicted did not change significantly at 12 months (mean decrease 3.8%predicted; 95% CI, – 2.4 to 10.0%; p = 0.228)**

Side effect	*N* = 40
•Diarrhea	4(10.0)
•Nausea	3(7.5)
•Elevated transaminases	3(7.5)
•Neuropathy	3(7.5)
•Skin rash	3(7.5)
•Hair loss	1(2.5)
•Other	2(5.0)
•None	24(60.0)

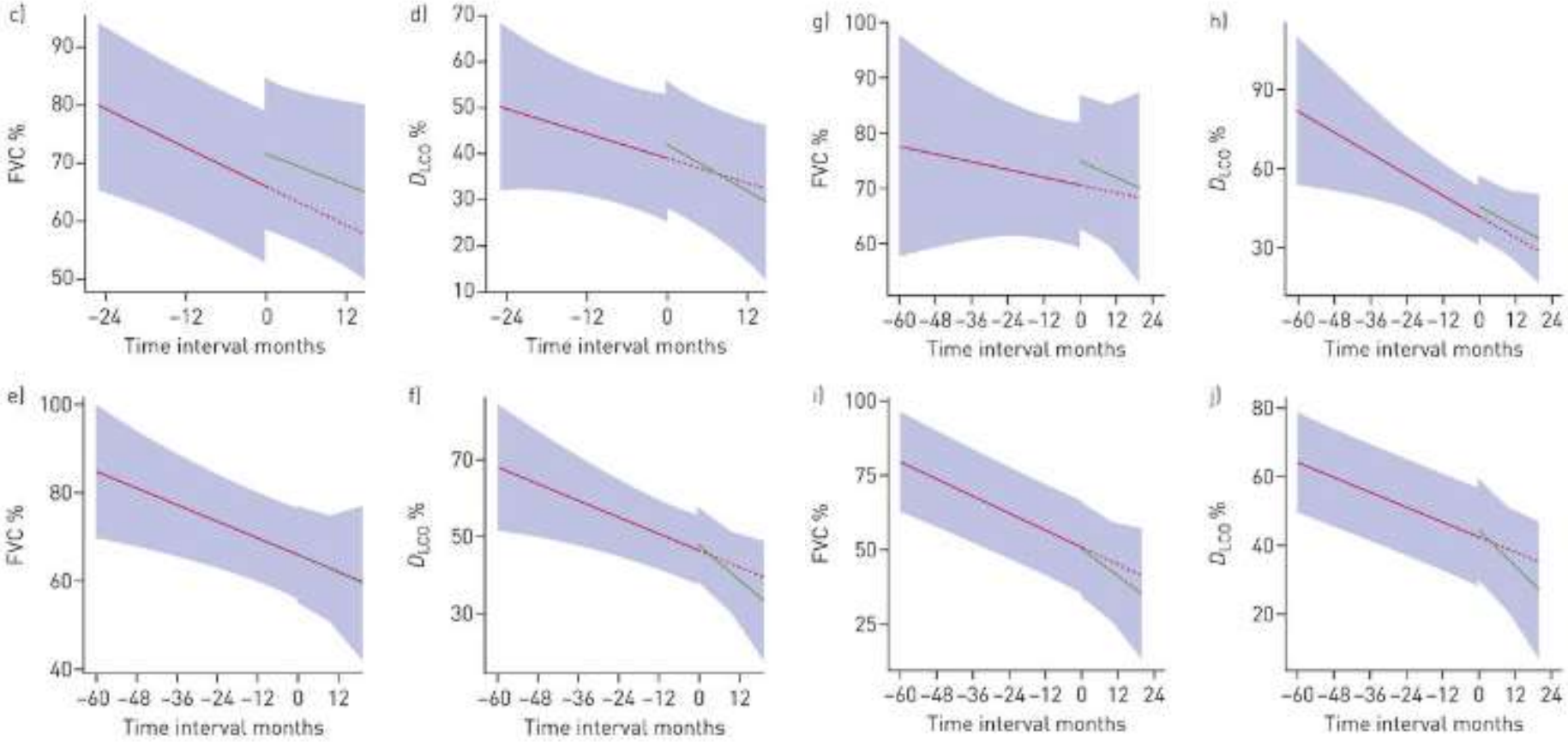
Impact of BAL lymphocytosis and presence of honeycombing on corticosteroid treatment effect in fibrotic hypersensitivity pneumonitis: a retrospective cohort study

- Retrospective analysis from 2005- 2016 of 91 fHP patients with baseline FVC and D_{LCO} 73.6±21.7% and 46.7±17.8%
- 58 patients (64%) had no honeycombing, 33 patients (36%) had honeycombing
- 67 (73.6%) were treated with CS, 20 patients (21.9%) CS + second line IS drugs
- 36 patients (40%) had high BAL-L, 55 had low BAL-L (60%)
- Low BAL-Lympho (<20%) : seen with increased honeycombing presence (low *vs* high BALL: 50.9% *vs* 13.9%, p<0.001)
- High BAL-L experienced an FVC increase of 5.66% (p=0.004) after CS initiation but rate of decline similar
- No CS effect was seen in the low BAL-L group (FVC % decline: p=0.96; D_{LCO} % decline: p=0.33)

De Sadeleer LJ etal., Eur Respir J. 2020 Apr 23;55(4):1901983



- low BAL-L and honeycombing presence were associated with poor 10-year survival (low BAL-L, HR 2.66, 95% CI 1.05–6.73, p=0.038; honeycombing presence, HR 3.80, 95% CI 1.66–8.73, p=0.002)



c) FVC high BAL Lympho **d)** D_{LCO} high BAL lympho **e)** FVC low BAL lympho

f) D_{LCO} low BAL lympho **g)** FVC in patients without honeycombing

h) D_{LCO} in patients without honeycombing **i)** FVC in patients with honeycombing

j) D_{LCO} trajectory in patients with honeycombing.

- Management of hypersensitivity pneumonitis is influenced by the presence of fibrosis and the presentation of the disease.
- Acute presentation and non fibrotic phenotype have been treated with antigen avoidance in HP due to known antigens & observation with or without steroids
- AZA and MMF have shown to be of benefit in slowing FVC / DLCO decline in some studies, and not beneficial in some
- Chronic hypersensitivity penumonitis treatment does not have strong evidence/recommendation. Treatment with long term steroids has not shown to be very beneficial in the fibrotic phenotype.
- Combined IS & Leflunomide may be beneficial in early chronic disease but if tolerated by patient
- Steroid sparing drugs which halt or reverse the disease still remains elusive

SARCOIDOSIS

Roflumilast (Daliresp®) to reduce acute pulmonary events in fibrotic sarcoidosis: a multi-center, double blind, placebo controlled, randomized clinical trial

SARCOIDOSIS VASCULITIS and DIFFUSE LUNG DISEASES

- Fibrotic sarcoidosis , at least two acute episodes in the previous year were randomized to receive either roflumilast (500mcg OD) or placebo
- 28 subjects: 3 months of therapy, & 20 completed 1 year of therapy (10 each arm)
- The odds ratio for observing an acute event for roflumilast treated patients was 0.34 (95% CI: 0.157 to 0.756, Chi square=7.191, p=0.0073).
- The KSQ LUNG increased by more than 7 points in the roflumilast group ($p<0.05$) compared to minus 1.6 for the placebo patients (MCID4)

Effect of therapy on frequency of visits with an FEV-1 of less than 90% of best value

	Roflumilast	Placebo
% clinic visits without an event*	42 (74%)	28 (49%)
% clinic visits with an event	15 (26%)	29 (51%)

*Acute event is FEV-1 of 90% or less of maximal value. Chi Square=7.191, p=0.0073

Baughman RP etal., Sarcoidosis Vasc Diffuse Lung Dis. 2021;38(3):e2021035.

Spirometry and Quality of Life before and at end of treatment * of those who took at least three months of therapy

	Roflumilast initial		Roflumilast Follow-up		Placebo initial		Placebo Follow-up	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Spirometry								
FEV-1, L **	1.80	0.689	1.83	0.727	1.54	0.665	1.65	0.6633
FEV-1 % predicted	61.357	17.4867	63.929	20.6154	59	22.2987	64.214	23.5607
FVC, L	2.668	1.0126	2.631	1.009	2.446	1.033	2.496	0.9457
FVC % predicted	70.429	20.564	70.714	22.3553	69.786	16.6834	73.571	17.0867
Quality of life								
KSQ LUNG	45.3	6.89	52.6 ¶	7.91	53.1	17.63	51.7	22.46
LCQ	14.0	1.86	15.6 †	2.15	14.0	4.21	15.4	4.74

FVC: forced vital capacity; FEV-1: forced expiratory volume one second; LCQ: Leicester cough questionnaire; KSQ: King's sarcoidosis questionnaire. *Last value moved forward. **Pre bronchodilators. ¶ Compared to Roflumilast initial $p<0.05$. † Compared to Roflumilast initial $p=0.07$

Results From a Phase 4, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Repository Corticotropin Injection for the Treatment of Pulmonary Sarcoidosis

- To evaluate the efficacy and safety of repository corticotropin injection in patients with pulmonary sarcoidosis
- Subjects received S/C RCI 80 Units twice/week (n = 27) or placebo (n = 28) for 24 weeks
- Efficacy was measured by glucocorticoid tapering, pulmonary function tests, chest imaging, patient-reported outcomes, and a novel sarcoidosis treatment score (STS)
- The study was terminated early due to low enrollment caused by the COVID-19
- Mean STS at week 24 showed greater improvement with RCI (1.4) compared with placebo (0.7) which increased to (1.8) vs (0.9) after 48 weeks.
- *Patients in RCI group showed early glucocorticoid tapering without relapse*

Mirsaeidi M etal., Pulm Ther. 2023 Jun;9(2):237-253

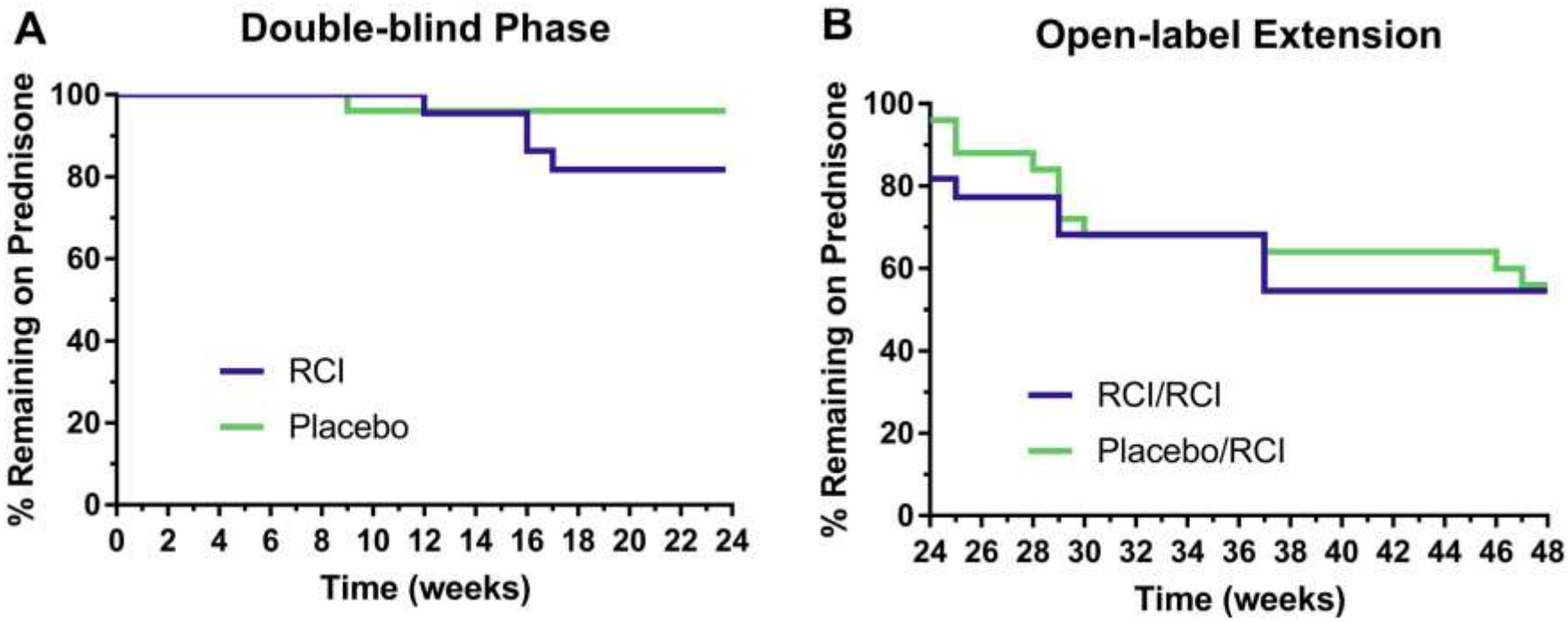

A
Double-blind Phase
% Remaining on Prednisone
100
80
60
40
20
0
RCI
Placebo
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (weeks)
B
Open-label Extension
% Remaining on Prednisone
100
80
60
40
20
0
RCI/RCI
Placebo/RCI
24 26 28 30 32 34 36 38 40 42 44 46 48
Time (weeks)

Table 2 Efficacy results for STS, pulmonary function tests, and patient-reported outcomes

Parameter	Double-blind phase (week 24)		Open-label extension (week 48)	
	RCI	Placebo	RCI/RCI	Placebo/RCI
Prednisone taper, % change from baseline[a] (95% CI)	− 57.3 (− 71.2 to − 43.4); n = 25	− 58.6 (− 70.5 to − 46.7); n = 25	− 75.7 (− 90.5 to − 60.95); n = 18	− 70.1 (− 86.6 to − 53.6); n = 23
Baseline mean prednisone dose, mg (95% CI)	14.5 (11.5 to 17.5); n = 27	11.6 (8.8 to 14.5); n = 28	15.7 (12.2 to 19.2); n = 22	11.8 (8.6 to 15.0); n = 25
Final mean prednisone dose, mg (95% CI)	7.3 (3.5 to 11.1); n = 25	4.9 (3.1 to 6.7); n = 25	5.3 (1.1 to 9.4); n = 18	3.4 (1.6 to 5.2); n = 23
STS, mean (SD) [95% CI]	1.4 (2.2) [0.5 to 2.3]; n = 25	0.7 (2.3) [− 0.2 to 1.6]; n = 23	1.8 (2.0) [0.8 to 2.8]; n = 15	0.9 (2.2) [− 0.1 to 1.9]; n = 20
Lung FVC				
Mean (SD) [95% CI] change from baseline	2.74 (5.2) [0.6 to 4.9]; n = 23	2.41 (7.6) [− 0.8 to 5.6]; n = 22	1.14 (4.7) [− 1.2 to 3.4]; n = 16	3.30 (8.9) [− 0.6 to 7.2]; n = 20
Improvement ≥ 5%, n (%)	10 (37.0); n = 27	7 (25.0); n = 28	2 (12.5); n = 16	6 (30.0); n = 20

[Diffuse Lung Disease Original Research]

CHEST

A Pilot Randomized Trial of Transdermal Nicotine for Pulmonary Sarcoidosis

- Double-blind, controlled study nicotine patch treatment vs placebo
- Non fibrotic sarcoidosis n=40, **baseline FVC% nicotine (86%,3.3L), placebo78%(2.9L)**
- Only prednisolone < 10mg/day was allowed & no 2nd Immunosuppressant
- **7mg→14mg→21mg patch**
- At 26-weeks, mean FVC decreased by 2.4% (70 mL) in the placebo group and increased by 2.1% (70 mL) in the nicotine group, for a mean treatment effect of 140 mL (95% CI, 10-260)
- Too small numbers, it was carried out to create path for a stage 3 trial

Crouser ED etal., Chest. 2021 Oct;160(4):1340-1349

DIFFUSE LUNG DISEASE

Is Nicotine Treatment Well Tolerated and Will It Improve Lung Function in Patients With Active Pulmonary Sarcoidosis?

STUDY DESIGN

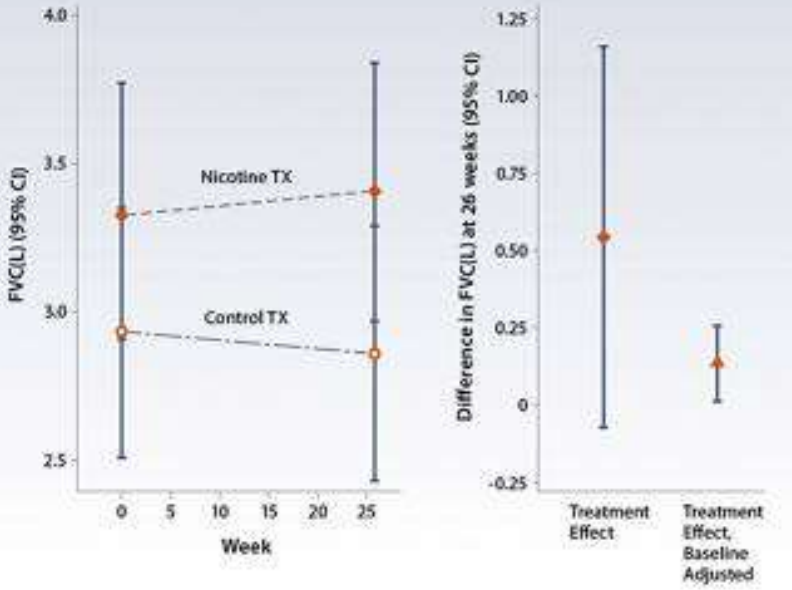
- Randomized, double-blind, controlled pilot trial
- **50 adults** with active pulmonary sarcoidosis
- Nicotine patch 21mg daily for 24 weeks

RESULTS

FVC increased 2.1% in treatment group and decreased 2.2% in placebo group (**net increase** of 140mL; 95% CI 10-260mL)

Fatigue Assessment Score was lower on average in nicotine group at 26 weeks (-2.99; -7.10, 1.12), although not statistically significant (p=0.15)

(Right) Average FVC at baseline and at 26 weeks and *(Far Right)* average FVC difference at week 26



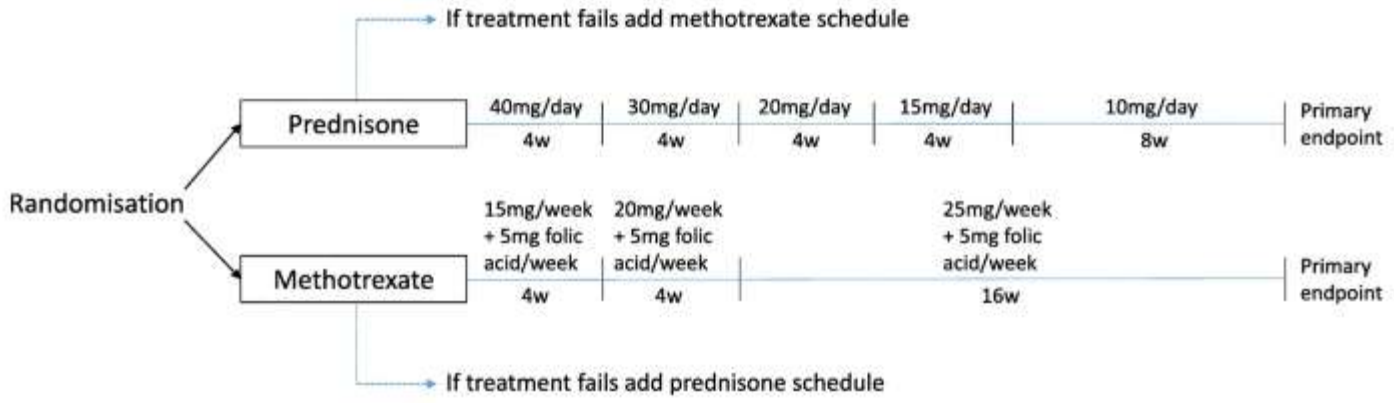
Nicotine treatment is well tolerated in patients with active pulmonary sarcoidosis and preliminary findings in this pilot study suggest it may reduce disease progression based on FVC.

Crouser ED, et al. *CHEST* October 2021 | @journal_CHEST | https://doi.org/10.1016/j.chest.2021.05.031

Design of a randomized controlled trial to evaluate effectiveness of methotrexate versus prednisone as first-line treatment for pulmonary sarcoidosis: the PREDMETH study

BMC Pulmonary Medicine

- prospective, randomized, non-blinded, multi-center, non-inferiority trial:
- 138 treatment-naïve patients with pulmonary sarcoidosis , 24 weeks and followed for 2 yrs



- Recruitment ongoing

Crouser Edetal., Chest. 2021 Oct;160(4):1340-1349.j.chest.2021.05.031

- Treatment of sarcoidosis : glucocorticoids have been recommended as benficial in improving lung function and symptoms.
- **AZA** and **MTX** have been used 2nd line for patients who need a longer duration of therapy, and as steroid sparing agents
- **Infliximab** has also been used in a few studies and has shown to improve FVC
- Other drugs which have been used are **MMF, leflunomide, adalimumab**
- **RCI / Rituximab / JAK inhibitors** have also been advised in the ERS 2021 guideline to be used on a case to case basis
- **Nicotine patch , roflumilast** will need further studies before being included in the treatment regimen
- If methotrexate can be used as a 1st line agent will only be answered after successful RCT which can show its non inferiority/ superiority to time tested glucocorticoids

Investigational

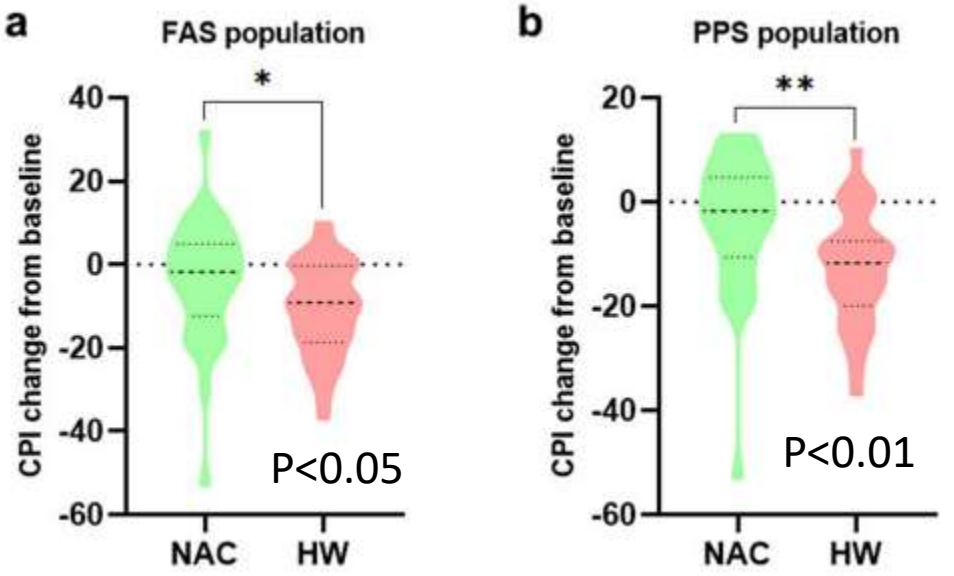
Efficacy and Safety of Hydrogen Therapy in Patients with Early-Stage Interstitial Lung Disease: A Single-Center, Randomized, Parallel-Group Controlled Trial

- ILD associated with pemphigus, bullous pemphigoid, scleroderma, lupus erytheromatosus
- 350 mL 1.6 ppm hydrogen-rich water twice a day (n=44) : NAC 600mg TID (n=43)
- Out of 87 (FAS), 75 completed study (PPS) Baseline : FVC 86%, DLCO 70-76%
- Change from baseline in HRCT & CPI was the primary endpoint
- FAS : CPI improvement significant ($P < 0.05$) but HRCT changes not significant
- PPS : CPI ($P < 0.01$) and HRCT significant improvement in HW group

Primary Endpoint	NAC Group	HW Group	Statistical Value	*P* value
FAS population-n (%)			5.619	0.060
Improving	17 (39.5%)	28 (63.6%)		
Stable	22 (51.2%)	12 (27.3%)		
Worsening	4 (9.3%)	4 (9.1%)		
PPS population-n (%)			9.676	0.008
Improving	15 (39.5%)	27 (73.0%)		
Stable	20 (52.6%)	7 (18.9%)		
Worsening	3 (7.9%)	3 (8.1%)		

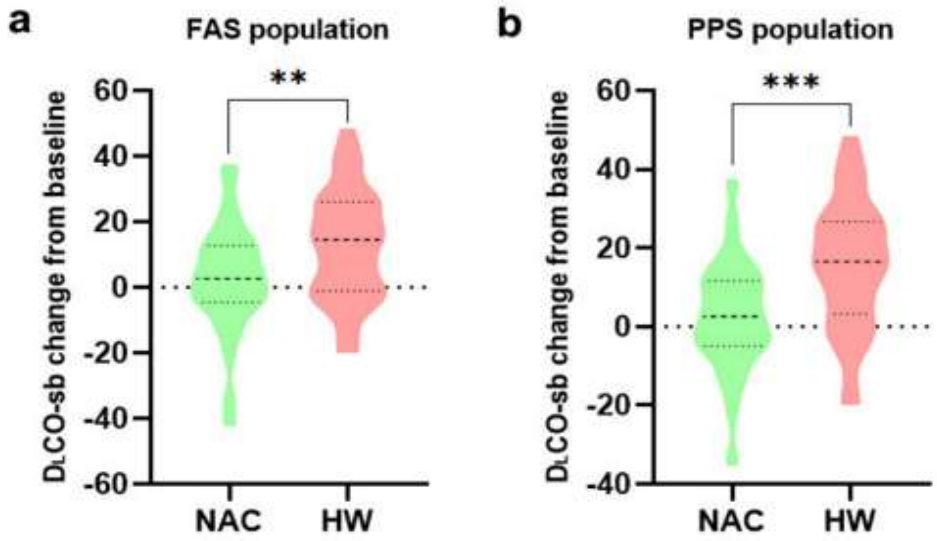
Abbreviations: FAS, full analysis set; PPS, per protocol set; NAC, N-Acetylcysteine; HW, hydrogen-rich water.

Tang C etal.,Ther Clin Risk Manag. 2023 Dec 11;19:1051-1061.



Changes from baseline in CPI in FAS (a) & PPS (b)

Significant reduction in CPI was observed in the HW group vs NAC group : in both the FAS ($P < 0.05$,) and PPS populations ($P < 0.01$)



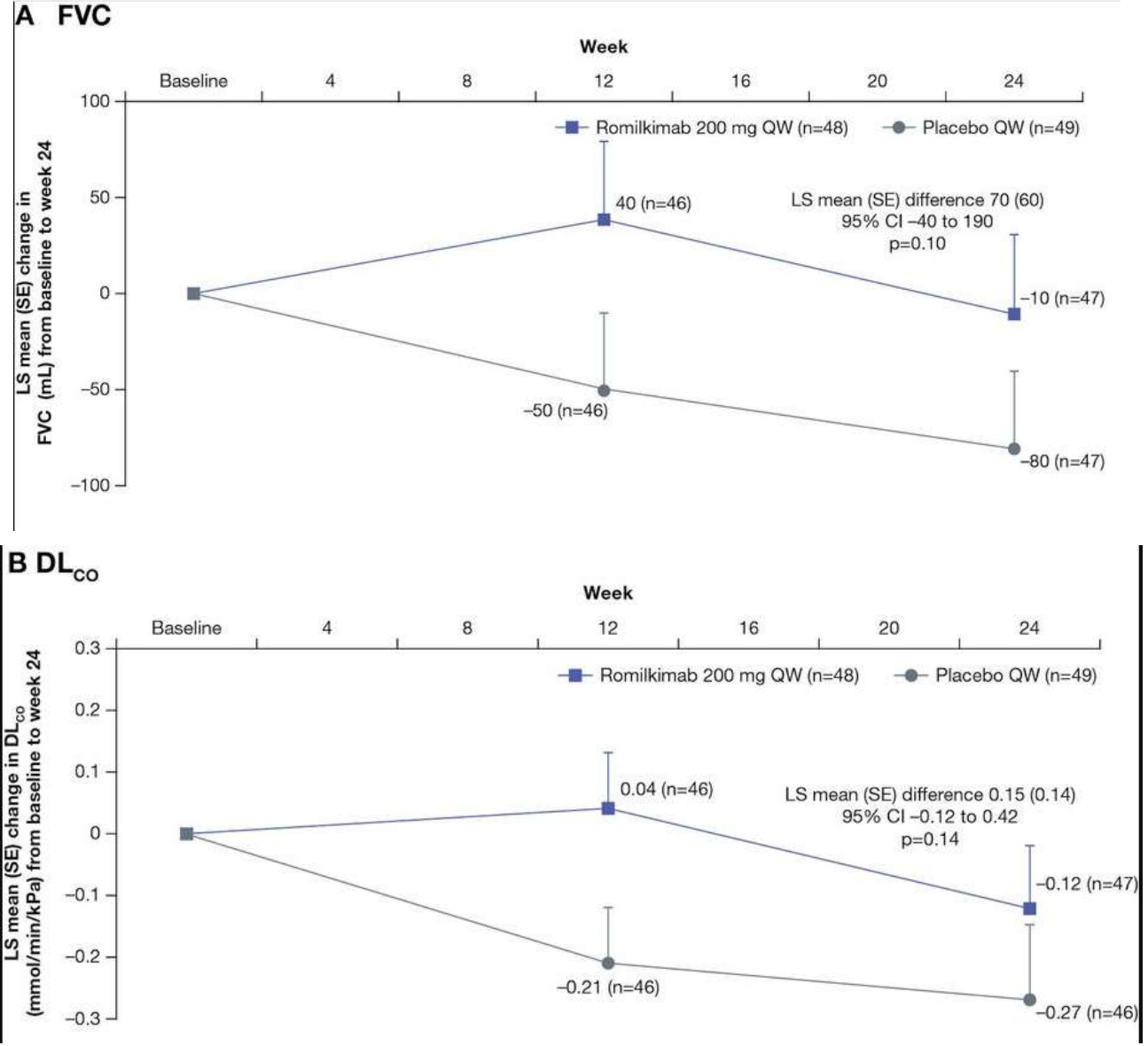
Changes from baseline in DLCO-sb in FAS (a) and PPS (b)

Significant improvement in DLCO-sb was observed when hydrogen therapy was compared with NAC in the FAS ($P < 0.01$) and PPS populations ($P < 0.001$,)

A randomised, double-blind, placebo-controlled, 24-week, phase II, proof-of-concept study of romilkimab (SAR156597) in early diffuse cutaneous systemic sclerosis

- ≥18 years diagnosed with diffuse cutaneous SSc & with or without IS background therapy, were randomised (1:1) to subcutaneous romilkimab 200mg or placebo once a week for 24 weeks
- Primary endpoint : reduction in modified Rodnan skin score at week 24
- Secondary: change from baseline to week 24 in FVC & DLCO + others
- Baseline : Romilkimab vs placebo : FVC % 96 vs 89, DLCO% 66 vs 72
- Background IS : Mtx (25% vs 43%), MMF (21% vs 14%), AZA (8% vs 2%)
- Patients with TB gold quantiferon positive results were excluded
- Primary endpoint analysis was statistically significant

Allanore Y etal., Ann Rheum Dis. 2020 Dec;79(12):1600-1607. doi: 10.1136/annrheumdis-2020-218447.



- This study is limited by a relatively short treatment duration, which may not have permitted the detection of significant differences

CD19-Targeting CAR T Cells for Myositis and Interstitial Lung Disease Associated With Antisynthetase Syndrome

- Case report of a 41/m patient with antisynthetase syndrome with progressive myositis and ILD refractory to available therapies (including rituximab and azathioprine)
- Treatment with CD19-targeting-chimeric antigen receptor (CAR) T cells
- 8 months after treatment: Physician Global Assessment, muscle and pulmonary function tests improved, no detectable signs of myositis on MRI.
- Serum muscle enzymes and interleukins normalised

Pecher AC,etal., JAMA. 2023 Jun 27;329(24):2154-2162.

NINSARC

- Nintedanib in fibrotic sarcoidosis : being done at our institute

SUMMARY

- Management of ILD till now is based on recommendations which are backed by limited evidence
- More studies are required to establish strong guidelines
- Cornerstone of therapy is based on clinical experience and with limited data available