EULAR Highlights- Systemische Sklerose/Myositis

Oliver Distler

Zurich, 29.06.2023

Disclosures

Oliver Distler Speakers bureau and/or Consultant: 4P-Pharma, Abbvie, Acceleron, Alcimed, Altavant, Amgen, AnaMar, Arxx, AstraZeneca, Baecon, Blade, Bayer, Boehringer Ingelheim, Corbus, CSL Behring, Galderma, Galapagos, Glenmark, Gossamer, iQvia, Horizon, Inventiva, Janssen, Kymera, Lupin, Medscape, Merck, Miltenyi Biotec, Mitsubishi Tanabe, Novartis, Prometheus, Redxpharma, Roivant, Sanofi and Topadur. Patent issued “mir-29 for the treatment of systemic sclerosis” (US8247389, EP2331143), Grant/research support from: BI, Kymera, Mitsubishi Tanabe. Cofounder Citus AG.

Three different definitions of ILD progression

FVC decline>5% over 12 months

PPF guideline criteria[1]:

Worsening in 2/3 domains over 12 months:

1. Respiratory symptoms
2. Absolute decline in FVC >5% or in DLCO >10%
3. Radiological disease progression

PF-ILD INBUILD[2]:

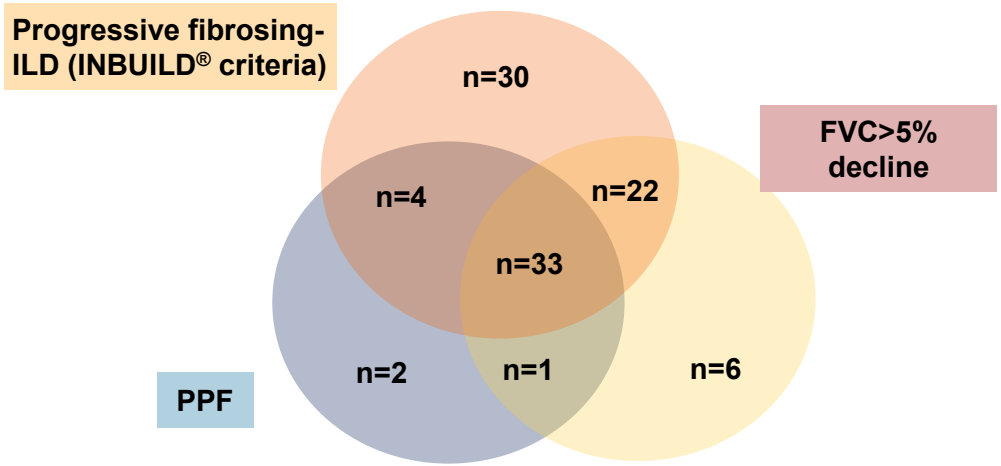
Worsening within 24 months:

1. Relative FVC decline ≥10%
2. Relative FVC decline 5-9% and worsening of respiratory symptoms or increased lung fibrosis on HRCT
3. Worsening of respiratory symptoms and increased lung fibrosis

[1]Raghu et al, Am J Respir Crit Care Med 2022 May 1;205(9):e18-e47; [2]Flaherty KR et al. N Engl J Med 2019;381:1718-27;

The prevalence of progressive ILD varied depending on the applied definition for ILD progression

231 SSc-ILD patients from Oslo (n=159) and Zurich (n=72)

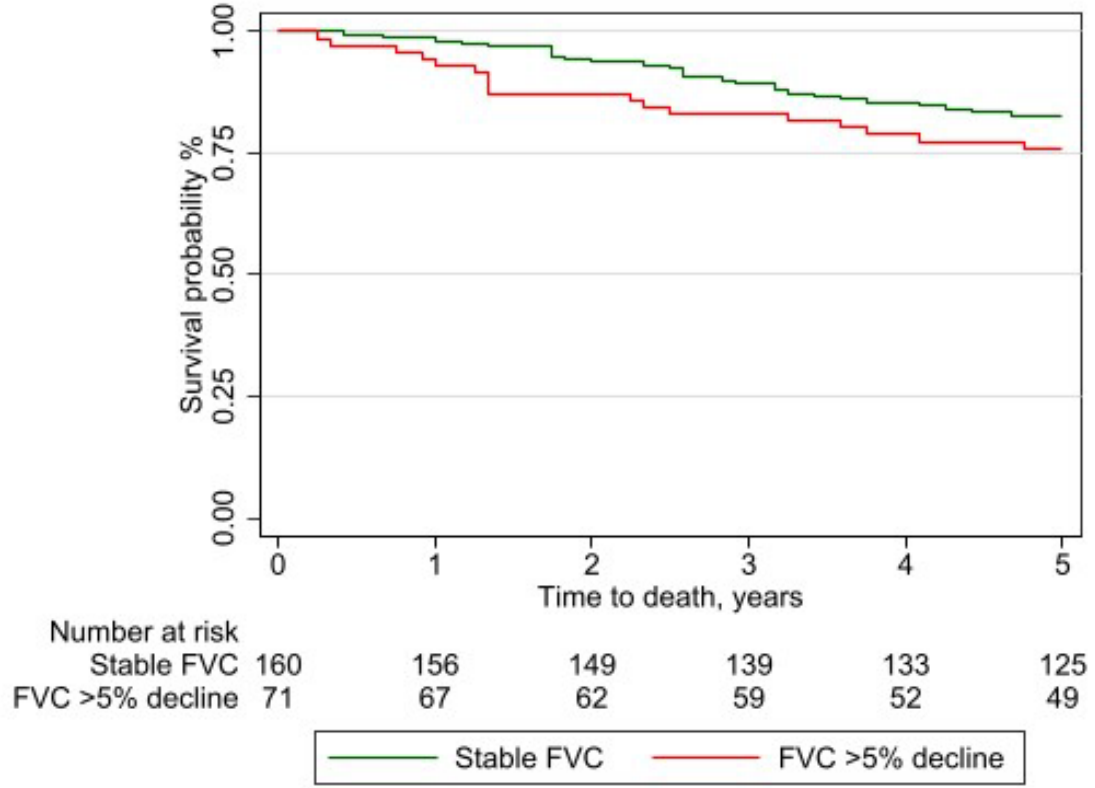


Definition	N (%)
FVC >5% decline	71 (31%)
Progressive fibrosing-ILD (INBUILD® criteria)	89 (39%)
PPF	39 (17%)

Clinical characteristics of the 231 SSc patients varied depending on defintion of progressive disease

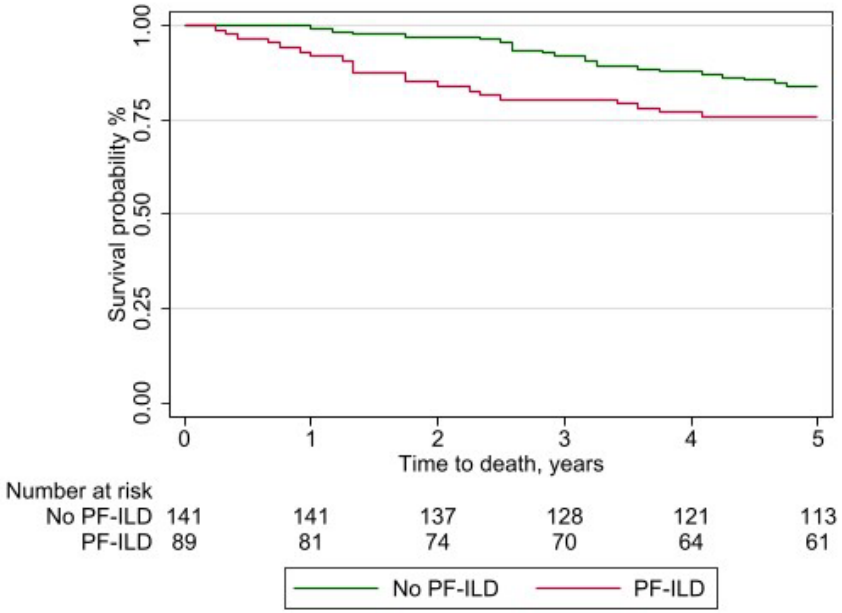
	FVC decline>5% N=71	PPF N=39	PF-ILD N=89
Male sex, n (%)	20 (28)	11 (28)	27 (30)
Age at onset, y (SD)	49 (14.8)	49 (13.5)	48 (13.0)
Disease duration<3y, n (%)	9.4 (11.2)	7.8 (8.8)	7.9 (8.9)
dcSSc, n (%)	36 (51)	22 (56)	46 (52)
ATA, n (%)	33 (47)	20 (51)	38 (43)
CRP↑, n (%)	7 (14)	2 (9)	7 (11)
FVC, % (SD)	93 (19.6)	88 (18.9)	89 (20.4)
DLCO, % (SD)	66 (16.3)	61 (16.4)	65 (17.7)
Functional class 3&4, n (%)	9 (19)	5 (18)	11 (18)
ILD>20%, n (%)	17 (26)	15 (44)	27 (34)
Ground glass, n (%)	28 (42)	22 (59)	44 (51)
O_2 desaturation, n (%)	6 (14)	6 (30)	9 (16)
Immunosuppressives, n (%)	20 (28)	18 (46)	38 (44)
Death, n (%)	32 (45)	18 (46)	39 (44)

FVC >5% decline predicts mortality in SSc-ILD

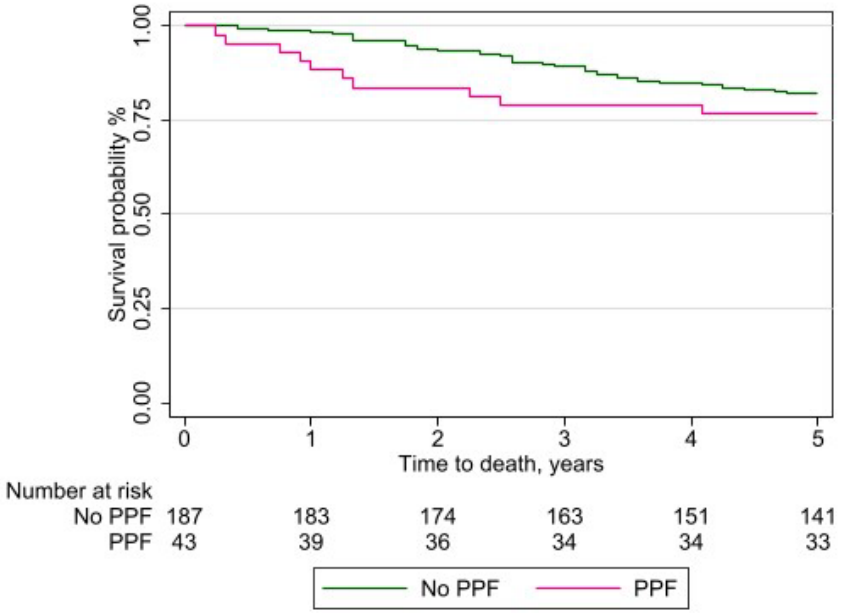


P= 0.031

PF-ILD but not PPF predicts long-term mortality in SSc-ILD

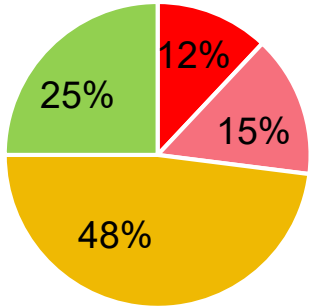


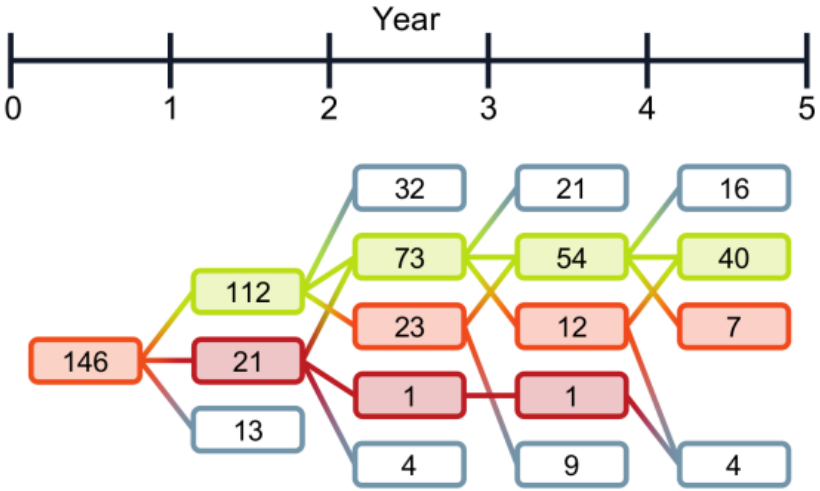
P= 0.012

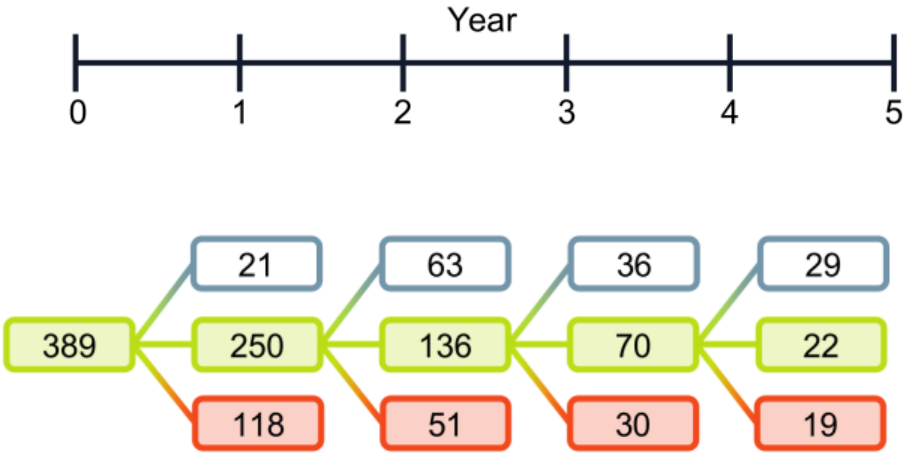


P= 0.112

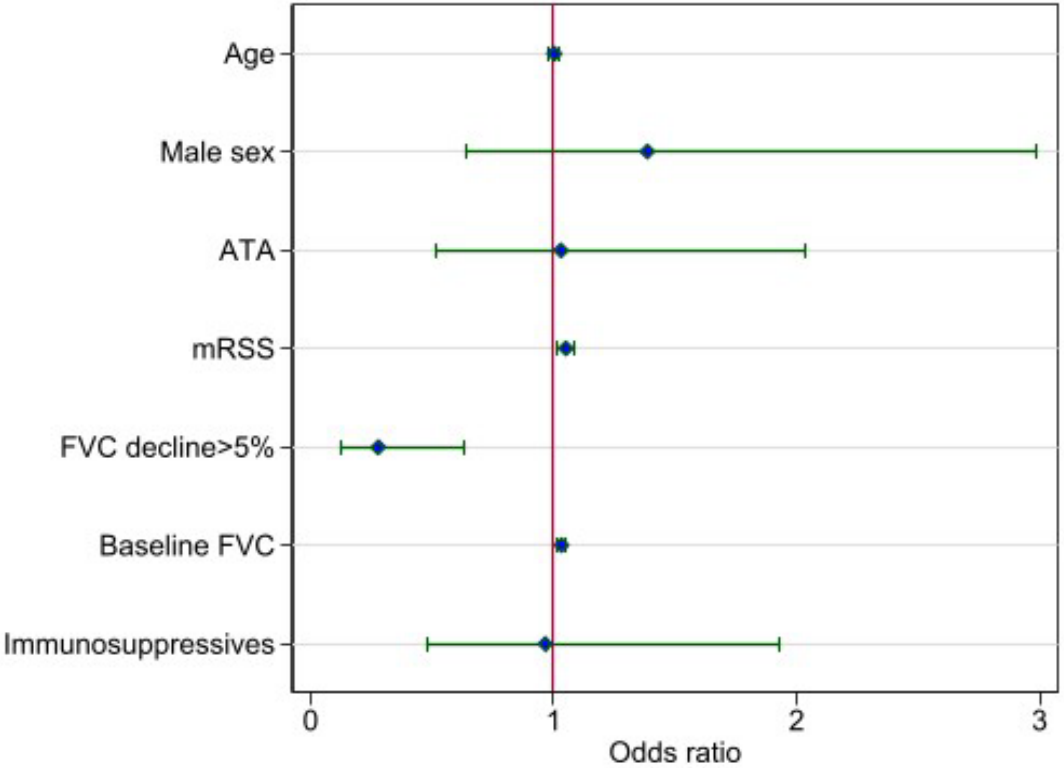
Significant progression happens in phases - continued significant progression is rare



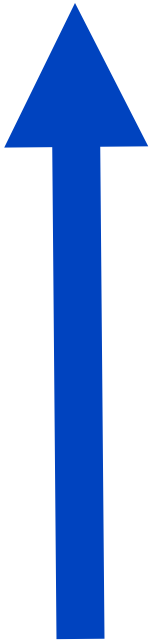




FVC decline predicts FVC stabilization independent of treatment in SSc-ILD



Oxford Centre for Evidence-Based Medicine: levels of evidence



1a	Systematic review (with homogeneity) of RCTs
1b	Individual RCT (with narrow confidence intervals)
1c	All or none study
2a	Systematic review (with homogeneity) of cohort studies
2b	Individual cohort study (including low quality RCT, e.g. <80% follow-up)
2c	'Outcomes' research; ecological studies
3a	Systematic review (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case series (and poor quality cohort and case-control study)
5	Expert opinion without explicit critical appraisal or based on physiology bench research or 'first principles'

https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009.

THERAPEUTIC ADVANCES in
Musculoskeletal Disease

Systematic Review

Calcineurin inhibitors in systemic sclerosis – a systematic literature review

Ther Adv Musculoskel Dis
2022, Vol. 14: 1–19
DOI: 10.1177/1759720X221092374

Nina N. Hofmann*, Robert A. Ambühl*, Suzana Jordan and Oliver Distler

Abstract

Objective: To review treatment effectiveness and adverse events of calcineurin inhibitors (CNIs) such as cyclosporin A (CsA) and tacrolimus in patients with systemic sclerosis (SSc).

Methods: A systematic literature search was performed on PubMed and Web of Science using the predefined keywords 'systemic sclerosis', scleroderma, cyclosporin*, and tacrolimus. Articles were eligible for inclusion, if SSc patients had been treated with CNIs and data on treatment effects were available.

Results: This systematic literature review identified 37 papers (19 case reports, 15 case series, 2 controlled studies, and 1 retrospective study) including 134 SSc patients treated with CNIs. In 34 of 37 papers, CsA was used. An improvement of skin fibrosis was observed in 77 of 96 (80.2%) patients using a wide variety of outcome measures and dose regimes. Both controlled studies showed significant improvements, one using a historical control group and one using a no-treatment control group. Improvement in pulmonary function tests (PFTs) occurred in 67.9% (19/28) of the patients who had reduced PFTs at baseline. In 58 (43.3%) cases, adverse renal events were reported, of which 7 (5.2%) were severe such as scleroderma renal crisis (SRC), CsA-associated nephropathy, or death by renal insufficiency. Adverse events led to dose reduction, treatment interruption, or withdrawal in 39 of 134 (29.1%).

Conclusion: In this systematic literature review, signals for potential effectiveness of CsA for skin and pulmonary fibrosis were found, but the evidence level of the identified studies was too low to allow robust conclusions. Randomized controlled double-blind trials are needed to conclude on the effectiveness of CNIs in SSc. Renal toxicity of CNIs was confirmed in this review and needs to be considered in the design of such studies.

A RCT comparing the efficacy of Tacrolimus with MMF in SSc-ILD (INSIST)

- **Design**: Single centre, open labelled, prospective randomized controlled pilot study (INSIST)
- **Setting:** Tertiary care rheumatology outpatient clinic at Post Graduate Institute of Medical Education and Research (PGIMER) in Northern India
- **Duration**- November 2021 to December 2022
- Ethical approval obtained from the institutional ethics committee
- **CTRI registration**: CTRI/2021/11/037864

Inclusion Criteria

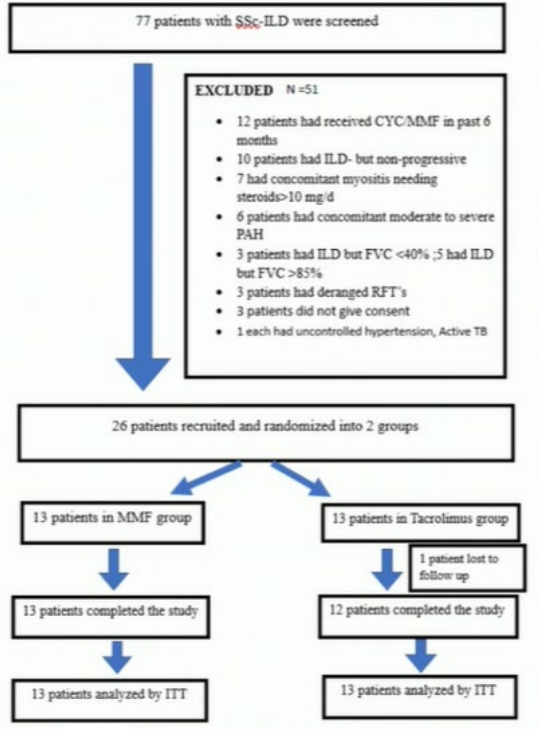
- Age 18-65 years
- Duration of SSc- <7 Years
- FVC- 40-85%
- HRCT- ILD
- Progressively declining lung function (FVC decline >10%) despite prior CYC/MMF (at least > 6 months previously), or on low dose steroids
- Symptoms attributable to ILD

Exclusion Criteria

- FVC < 40%
- S. Creat >1.2 mg/dl
- MMF/CYC in past 6 months
- Prednisolone >10mg/day
- Moderate/Severe PAH requiring drug therapy
- Significant Airflow obstruction (FEV1/FVC<0.65)
- Uncontrolled HTN despite 2 adequately dosed antihypertensives
- Active myositis
- Pregnant/breastfeeding mothers or planning conception
- Any prior use of Rituximab, tocilizumab

Primary outcome: Change of FVC% at week 24
Secondary outcome: mRSS, 6MWD, PROMs, ACR CRISS and safety

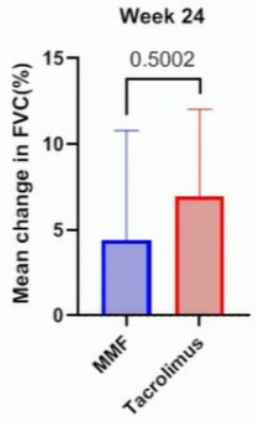
The INSIST trial study population

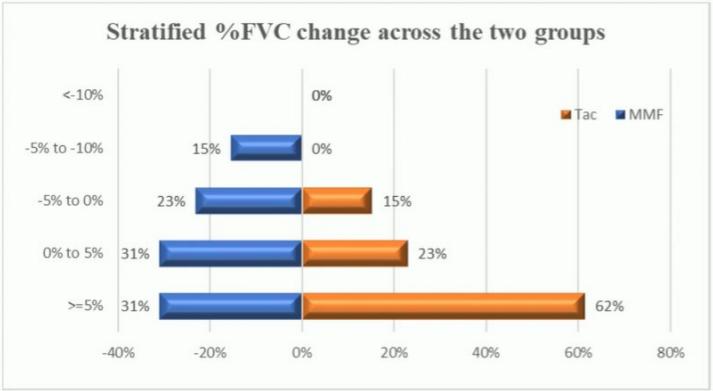


	Total (n=26)	Mycophenolate Mofetil (n=13)	Tacrolimus (n=13)	P value`
Age, mean (SD)	42 (9)	40.15 (7.9)	43.85 (9.9)	0.307
Women, n (%)	23 (88.5)	12 (92.3)	11 (84.6)	0.5
Duration from first non-RP symptom (years), median (IQR)	2.5 (1.4 -5.3	2.0 (1.5-4.5)	4.0 (1-7)	0.44
Disease duration <=3 years, n (%)	14 (53.8)	9 (69.2)	5 (38.5)	0.116
Systemic Sclerosis Diffuse, n (%) Limited, n (%)	 11 (42.3) 15 (57.7)	 8 (72.7) 5 (33.3)	 3 (27.3) 10 (66.7)	 **0.047**
Grade of Breathlessness (MMRC), median (IQR)	2 (2-2)	2 (2-2)	2(0.41)	0.762
Duration since SOB (years), median (IQR	1(0.5-3.3)	1 (0.6-1.5)	3 (0.5-5.2)	0.233
Past history of Immunosuppressive Treatment for SSc, n (%)	8 (30.8)	4 (15.4)	4 (15.4)	1.0
mRSS, median (IQR)	8.5 (3.7-19.5)	17 (6.5-22.5)	4 (3-18.5)	**0.08**
Anti Scl-70, n(%)	19 (73)	8 (27)	11	0.189
Anti- U1RNP, n(%)	6 (23.0)	3 (23.1)	3 (23.1)	0.637
S. Creatinine (mg/dl), median (IQR)	0.74 (0.3)	0.69 (0.27)	0.8 (0.37)	0.440
CRP (mg/L), median (IQR)	3.5 (2.1-5.4)	4.8 (1.8-5.3)	2.9 (2.0-5.4))	0.801

Both MMF and Tacrolimus showed an improvement of FVC at week 24

	Mycophenolate Mofetil (n=13)	Tacrolimus (n=13)	P value
Change in FVC (% predicted), mean (SD)	+ 4.4 (10.6)	+ 6.92 (8.4)	Difference 2.52%, 95% CI (-10.3 to 5.18); p-0.500





Efficacy and safety of Abatacept in myositis associated ILD

Clinical variable	Placebo (N=11)	Abatacept (N=9)
Age	57.7 [47.8-64.5]	49.7 [46.6-59.3]
Female	4 (36)	5 (56)
Non-Hispanic	11 (100)	9 (100)
Caucasian	10 (91)	7 (78)
Anti-synthetase antibody		
Jo-1	7	4
Non-Jo1	4	5
ILD status		
New onset	3 (27)	2 (22)
Chronic	8 (73)	7 (78)
Myositis status		
Inactive	5 (45)	2 (22)
Active	4 (37)	5 (56)
Not present	2 (18)	2 (22)
FVC%DLCO%	61 [53-78]49 [41-64]	66 [49-69]47 [38-52]
Prednisone	11 (100)	8 (88)
Mycophenolate	8 (73)	8 (88)
Azathioprine	0 (0)	1 (11)

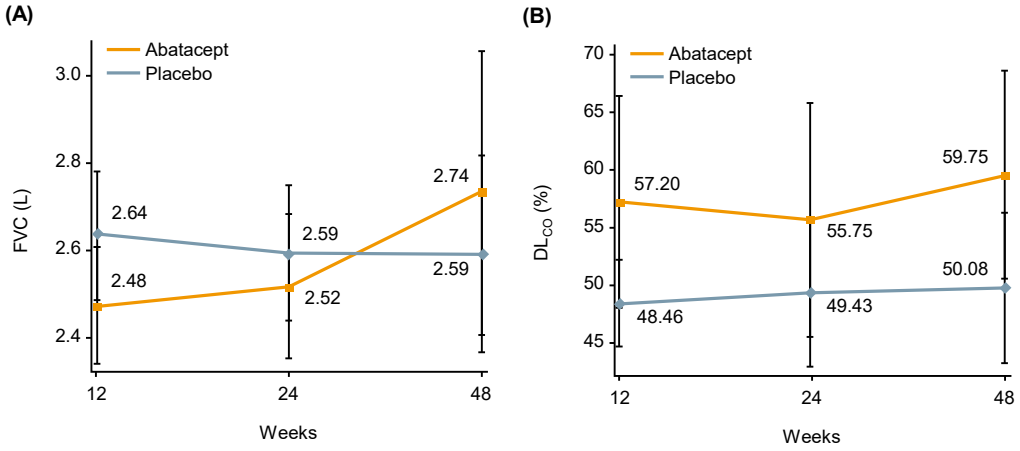
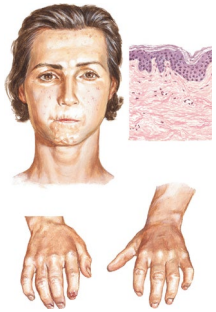


Figure. Pulmonary function test outcomes for patients receiving ABA or placebo:† (A) FVC change over time and (B) DL_{CO} change over time

Immunosuppression with targeted DMARDs reduces morbidity and mortality in pre-capillary pulmonary hypertension associated with systemic sclerosis: a EUSTAR analysis

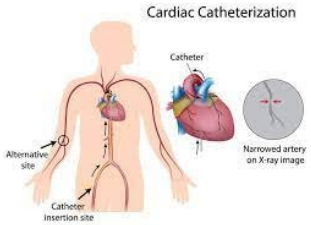
Bruni C, Tofani L, Fretheim H, Weber Y, Hachulla E, Carreira PE, Giuggioli D, Airò P, Siegert E, Muller-Ladner U, Matucci-Cerinic M, Riemekasten G, Simeon-Aznar CP, De Vries-Bouwstra J, Saketkoo LA, Distler JHW, Balbir-Gurman A, Castellví I, Zanatta E, Smith V, Denton C, Maurer B, Giollo A, Iannone F, Dagna L, Truchetet ME, Kuwana M, Allanore Y, Tanaka Y, Martin M, Rosato E, Georghiu AM, Del Galdo F, Solanki K, Vacca A, Resende C, Oliveira S, Czirják L, Baresic M, Cantatore FP, Riccieri V, Andréasson K, Chung LS, de Souza Müller C, Opris-Belinski D, Rednic S, Sfikakis P, Levy Y, Hsu V, Heitmann S, Henes J, Moroncini G, Iudici M, De Langhe E, Herrick A, Montecucco CM, Hoffmann-Vold AM, Distler O,
on behalf of the EUSTAR collaborators.

Materials and Methods I



SSc patients according to the 2013 ACR/EULAR criteria

EUSTAR center



RHC data

mPAP >=21 mmHg
PWP <=15 mmHg
PVR>=2 WU

Available information about treatments and outcomes

Exposure

IMS for at least 30 days, ongoing at PAH diagnosis or started anytime after PAH diagnosis

Conventional DMARDs (**csDMARDs**):

Prednisone>10 mg/day, MMF, MTX, AZA, CYC

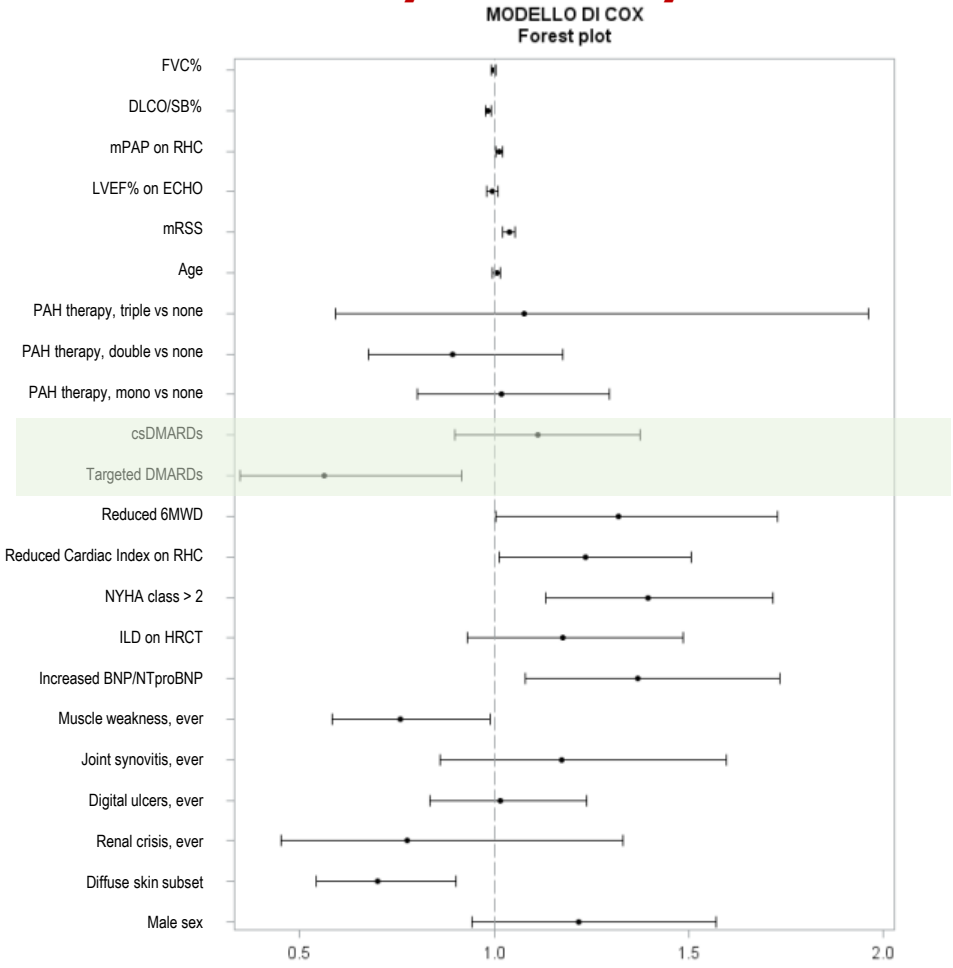
Targeted DMARDs:

RTX, TCZ, ABA, TNFi, JAKi

Outcome (at least 6 months observation)
time to morbidity/mortality, defined as
1. death or
2. worsening, defined as the first among these events:
- Decrease in the 6MWD of at least 15% from baseline
- Change from baseline to a higher NYHA class (or no change in patients who were in WHO functional class IV at baseline)
- RHF that did not respond to oral diuretic therapy
- Need for additional treatment for PAH
- initiation of treatment with IV or SC prostanoids
- lung transplantation
- atrial septostomy

csDMARD/Targeted DMARDs for morbidity-mortality

	ALL (N=755) – HR (95% CI)	P value
FVC%	-	
DLCO%	0.985 (0978-0.992)	<0.001
mPAP on RHC, mmHg	1.010 (1.001-1.019)	0.022
LVEF%	-	
mRSS	1.039 (1.024-1.054)	<0.001
Age, years	-	
VVD levels	-	
Sex female, n (%)	-	0.066
csDMARD	-	0.345
Targeted therapies	0.593 (0.364-0.966)	0.036
6MWD<440 m, n(%)	-	*0.055*
CI<2.5, n (%)	1.244 (1.022-1.513)	0.029
NYHA>2, n (%)	1.141 (1.151-1.736)	0.001
ILD on HRCT, n (%)	1.273 (1.019-1.589)	0.033
Increased BNP/NTproBNP, n (%)	1.354 (1.080-1.697)	0.008
Muscle weakness, n (%)	0.761 (0.590-0.982)	0.035
Arthritis, n (%)	-	
DU history, n (%)	-	
SRC history, n (%)	-	
Diffuse SSc, n (%)	0.715 (0.568-0.900)	0.004
Male sex, n (%)	-	

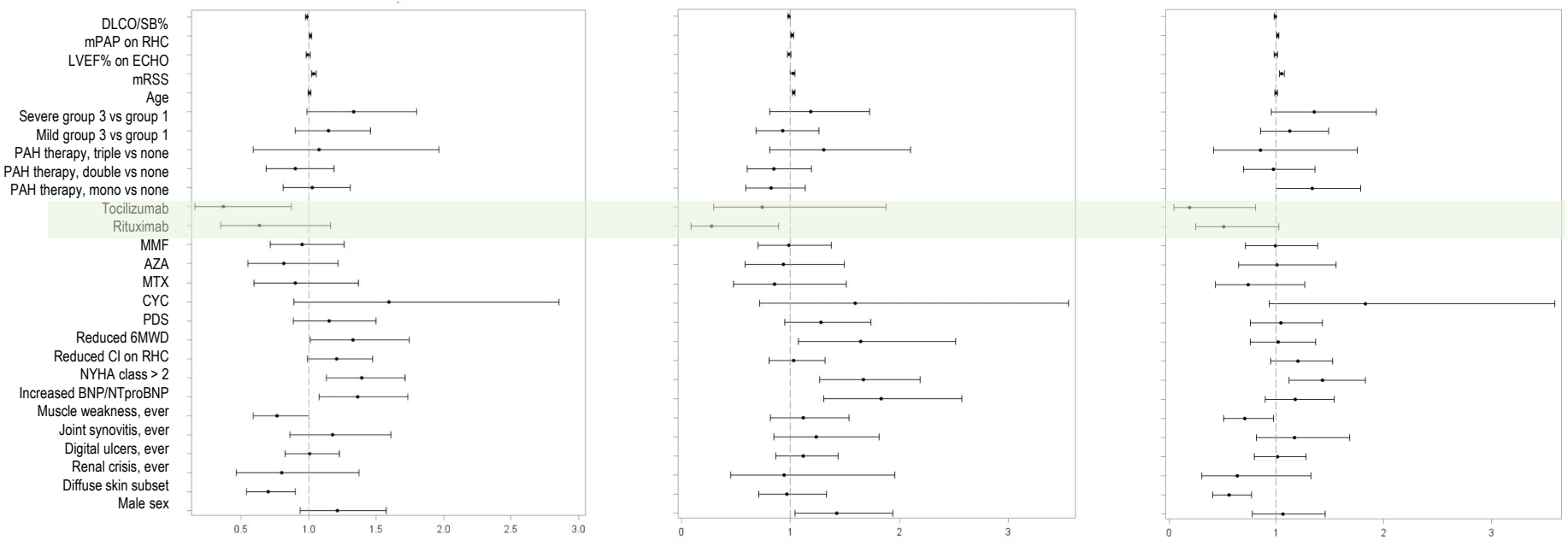


Single immunosuppressive therapy for

morbidity-mortality

mortality only

morbidity only



Conclusions

- Targeted DMARDs might have a role in treating SSc-associated pre-capillary PH, as they reduce the risk of morbidity and mortality events.

- Despite the well-known higher risk of mortality when precapPH is associated to presence of ILD (group 3), the effect of targeted DMARDs might be independent from the pathophysiological mechanisms leading to precapPH.

- In particular, while TCZ reduced the risk of combined morbidity/mortality and morbidity alone, RTX was associated with lower risk of mortality and a trend for lower morbidity.

- RCTs exploring these treatment strategies, in combination with precapPH VVD, should now be designed, using long-term morbidity and mortality outcomes.

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2023 Update of EULAR recommendations for the treatment of systemic sclerosis

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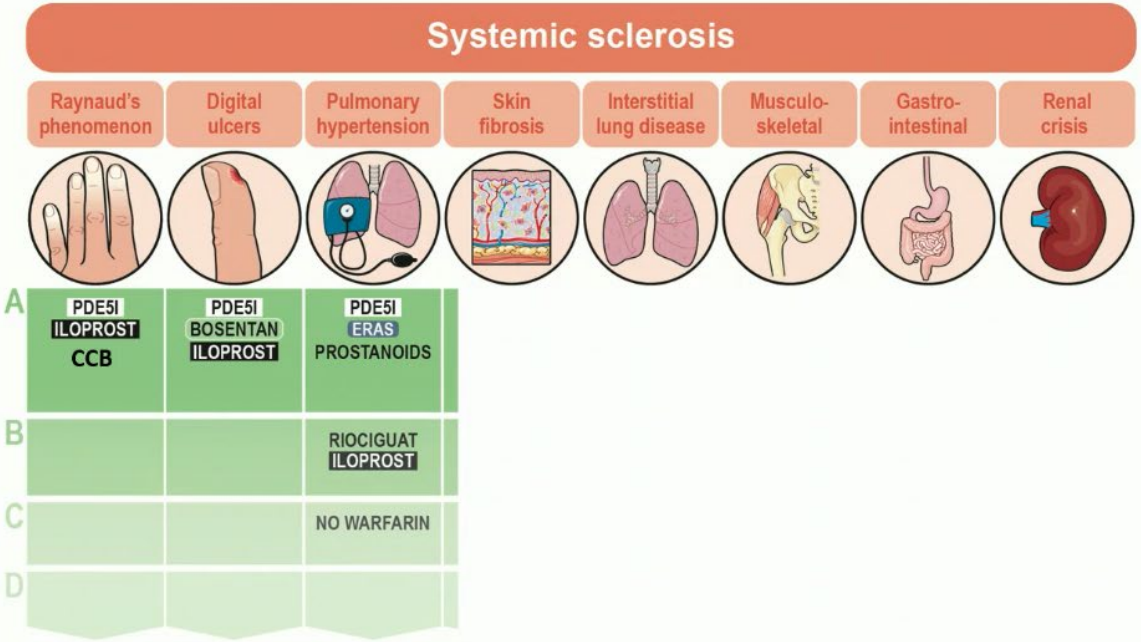
Results:

- 20 Recommendations (16 in 2017)



Results:

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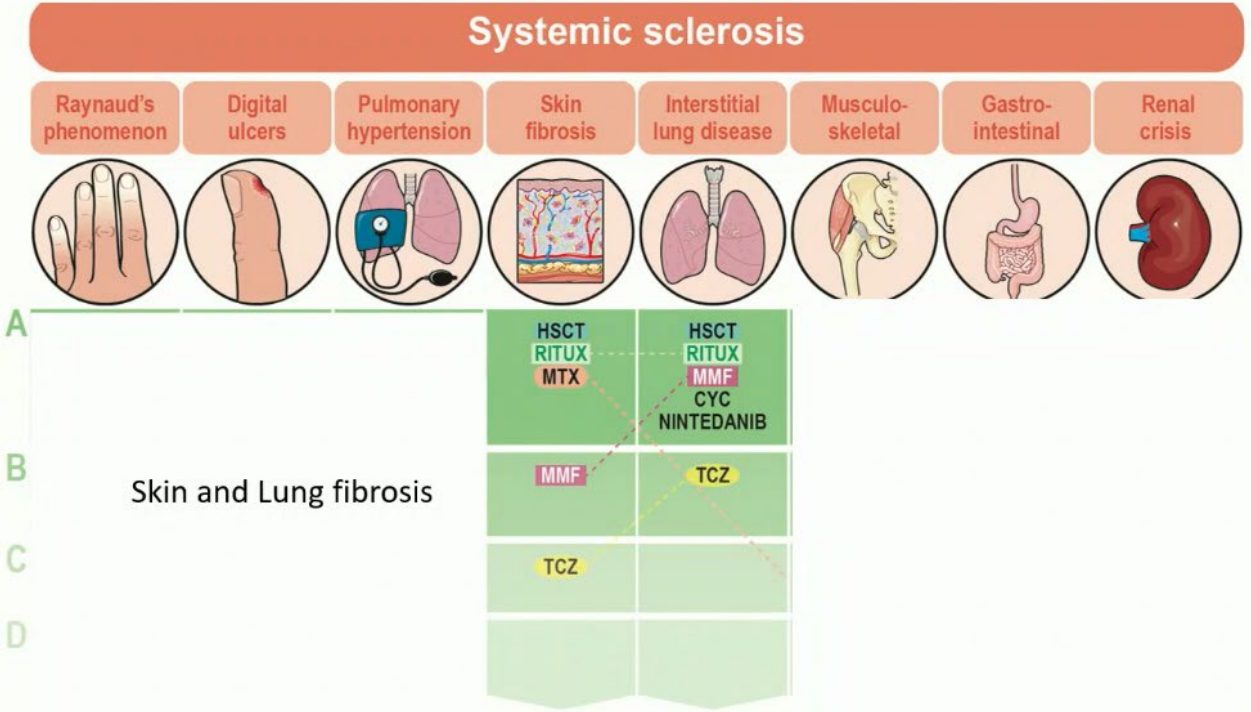

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Results:

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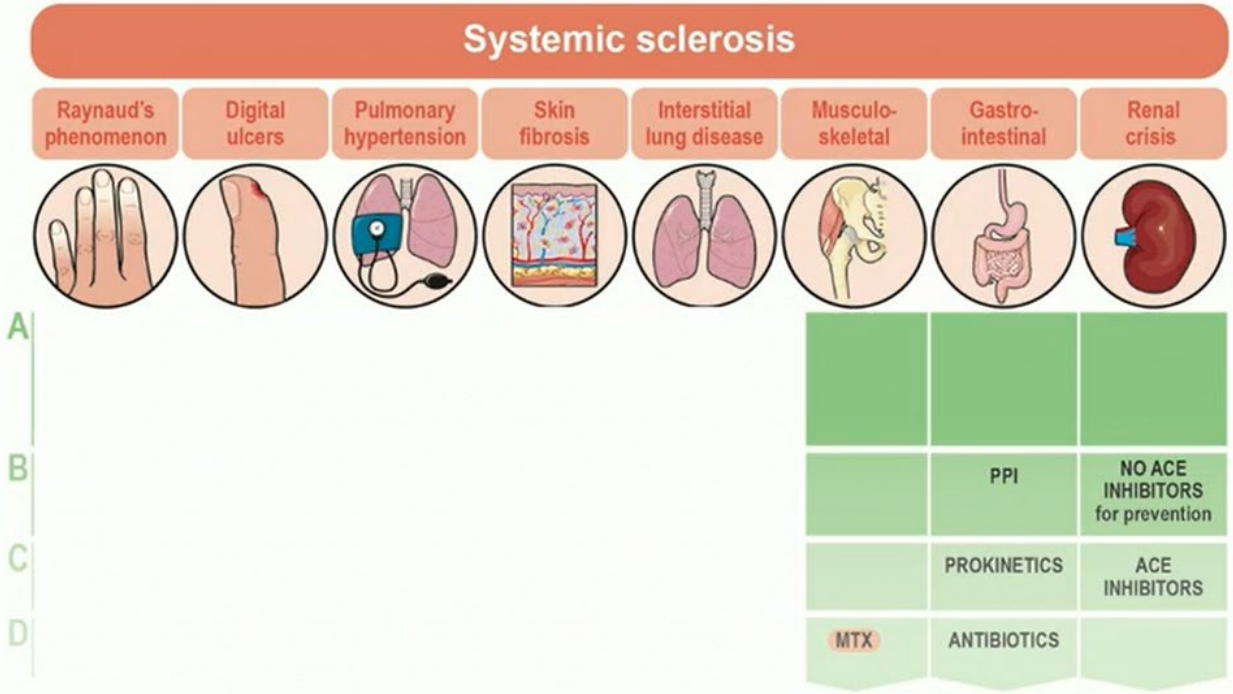

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