Νέες τάσεις στη θεραπεία του σκληροδέρματος

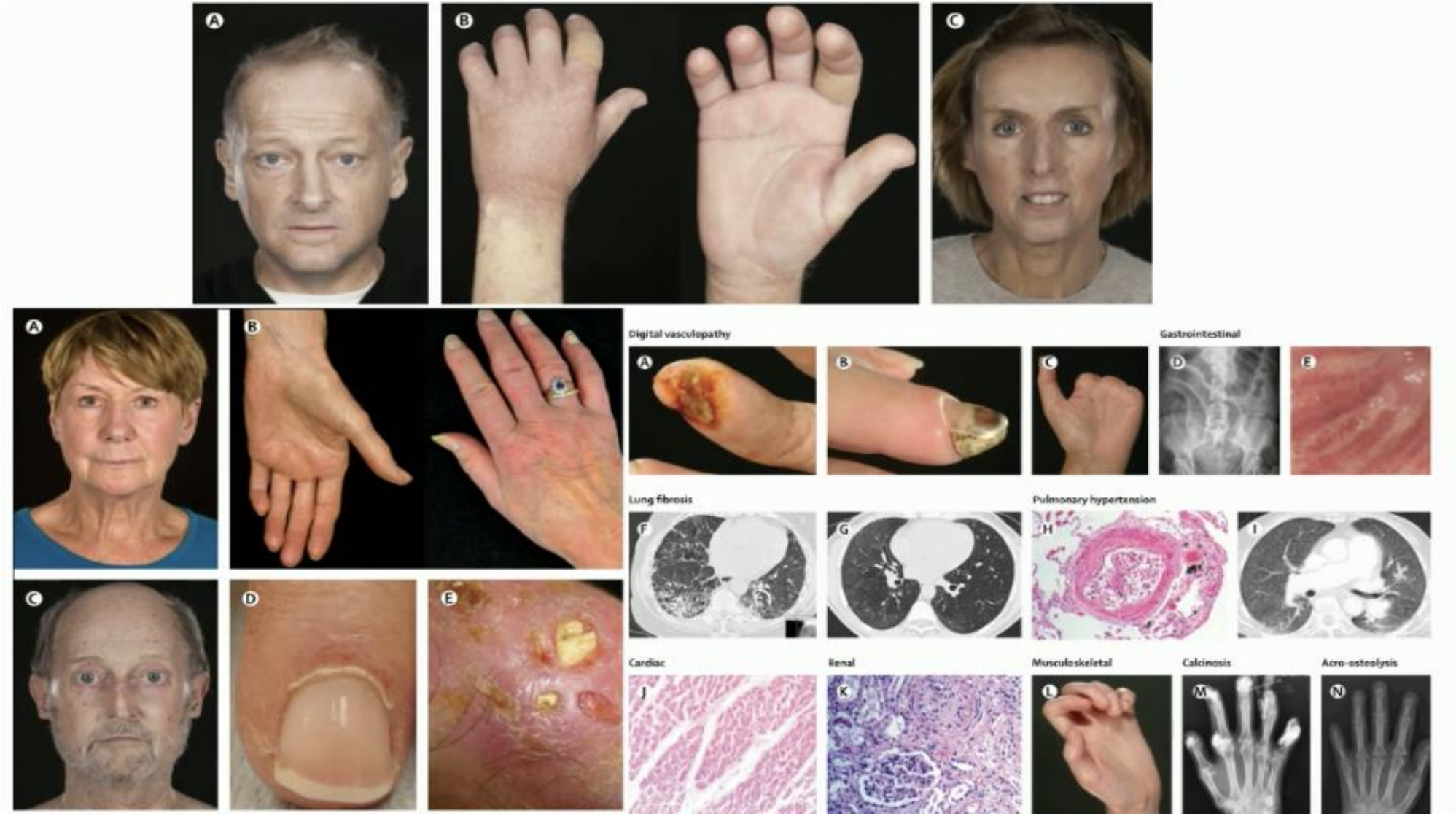
ΔΗΜΗΤΡΟΥΛΑΣ ΘΕΟΔΩΡΟΣ

Δ’ ΠΑΘΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ – ΙΠΠΟΚΡΑΤΕΙΟ ΝΟΣΟΚΟΜΕΙΟ ΘΕΣΣΑΛΟΝΙΚΗΣ

Σύγκρουση συμφερόντων
Conflict of interest

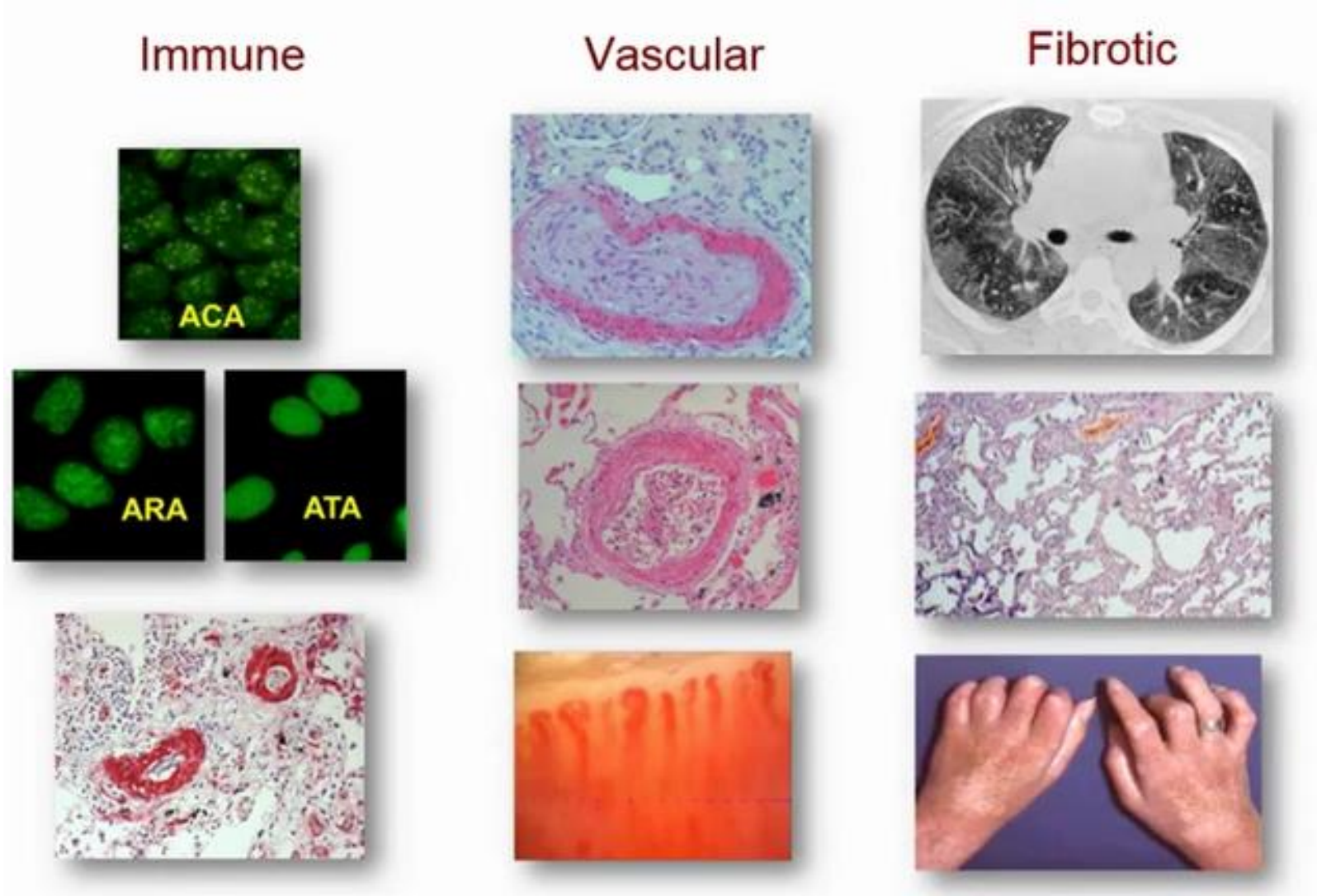
Παρούσα παρουσίαση: καμία

SSc is a multisystem disease

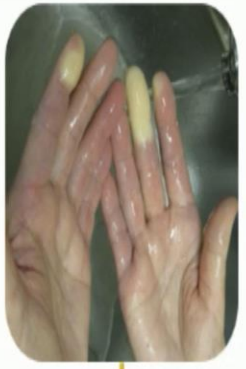


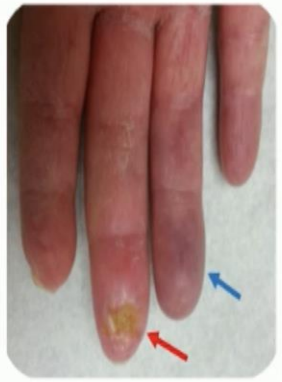
Denton C & Khanna D, Lancet 2017; 390(10103):1685-1699

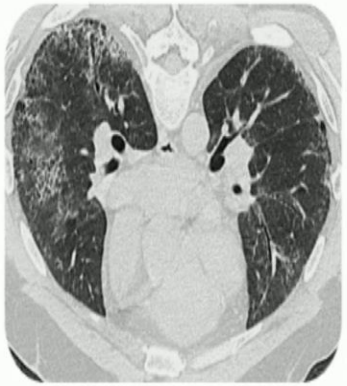
SYSTEMIC SCLEROSIS

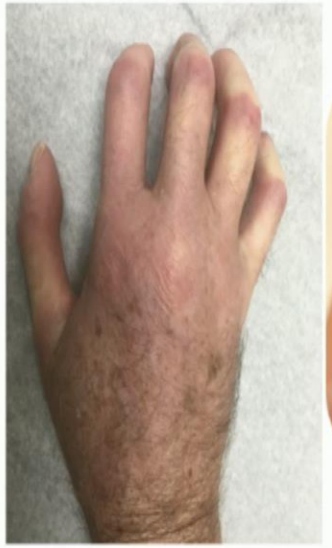


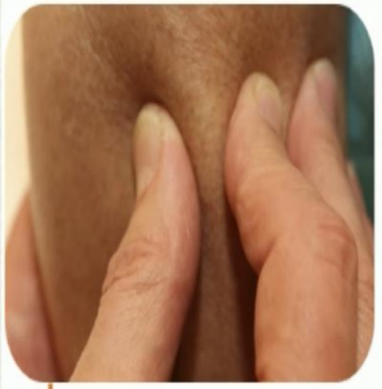
SSc Management







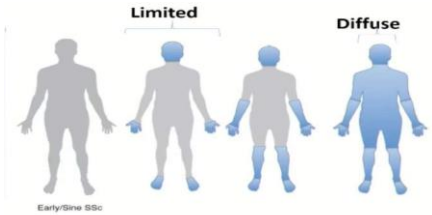




- Vasodilators

Supportive Care
- Anti-inflammatory medications
- H_2 blockers/ Proton pump inhibitors
- Occupational therapy

- Immunosuppressive medications
- Anti-fibrotic therapies
- Stem cell transplant



Skin subtypes predict clinical outcomes

Limited

Digital Ulcers

ILD: 20%

Vascular

Severe Raynaud's

PAH

Telangiectasia

Calcinosis
Raynaud's
Esophagus
Telangiectasia

Better survival

Diffuse

Rapid skin progression
Worse Clinical Outcomes

Fibrotic

Friction Rubs

Renal Crisis

Contractures

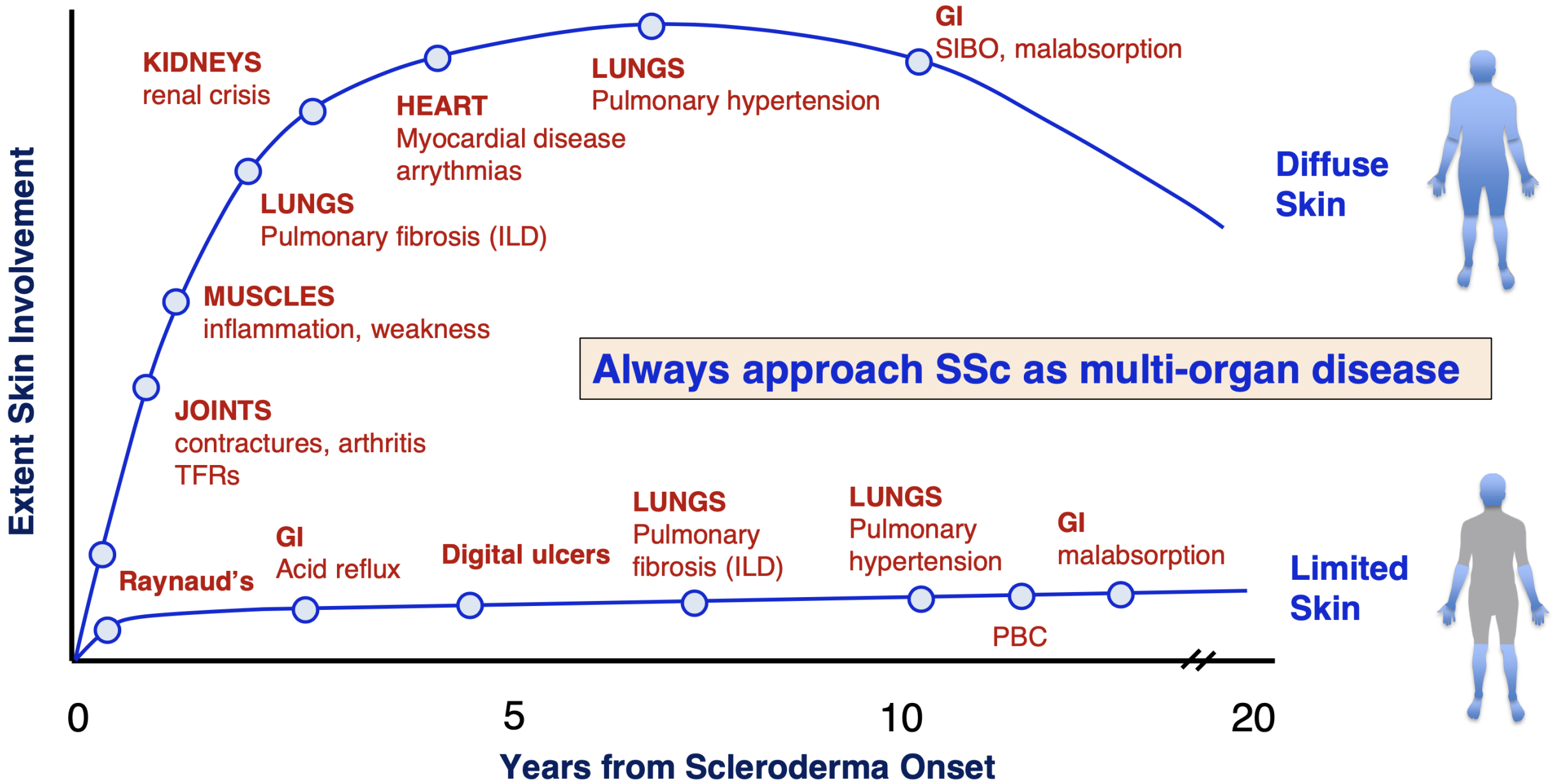
Skin

ILD

Multisystem

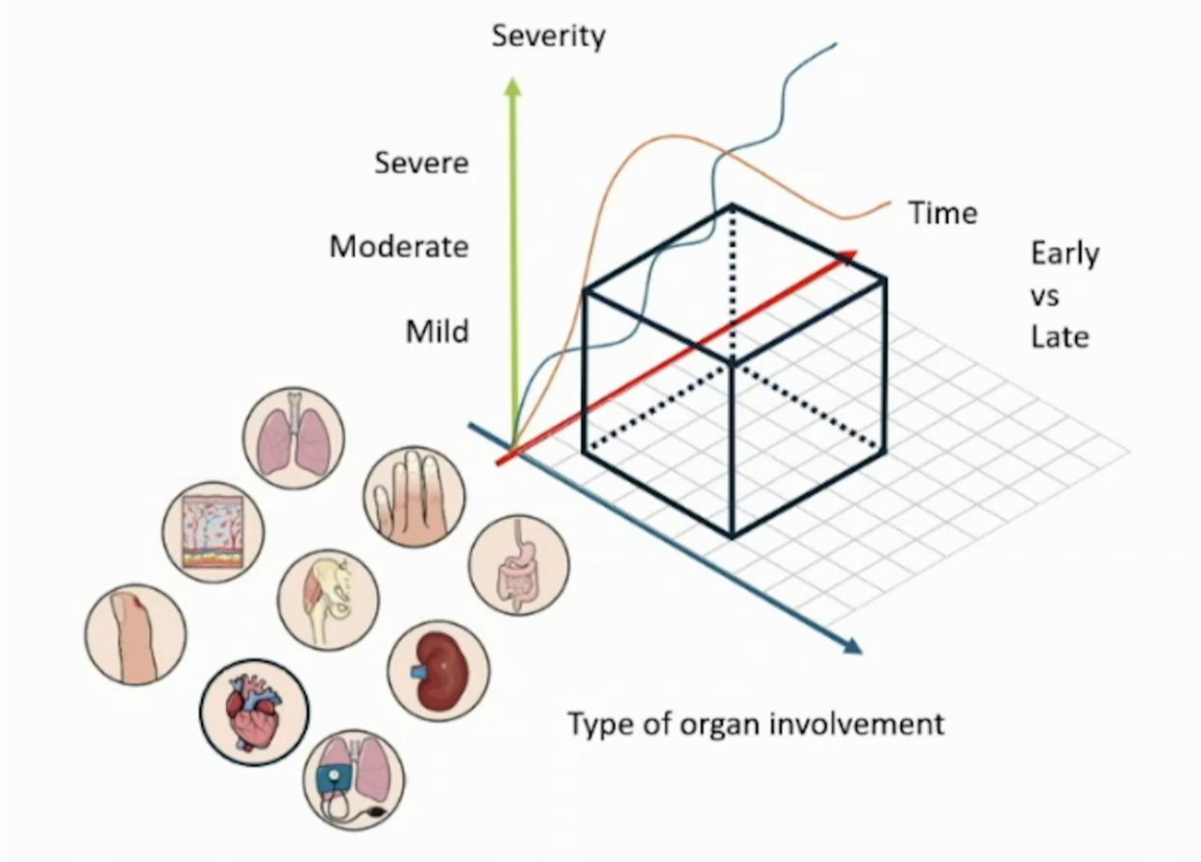
Worse Disease and Mortality

Timing of Skin and Organ Involvement In Scleroderma



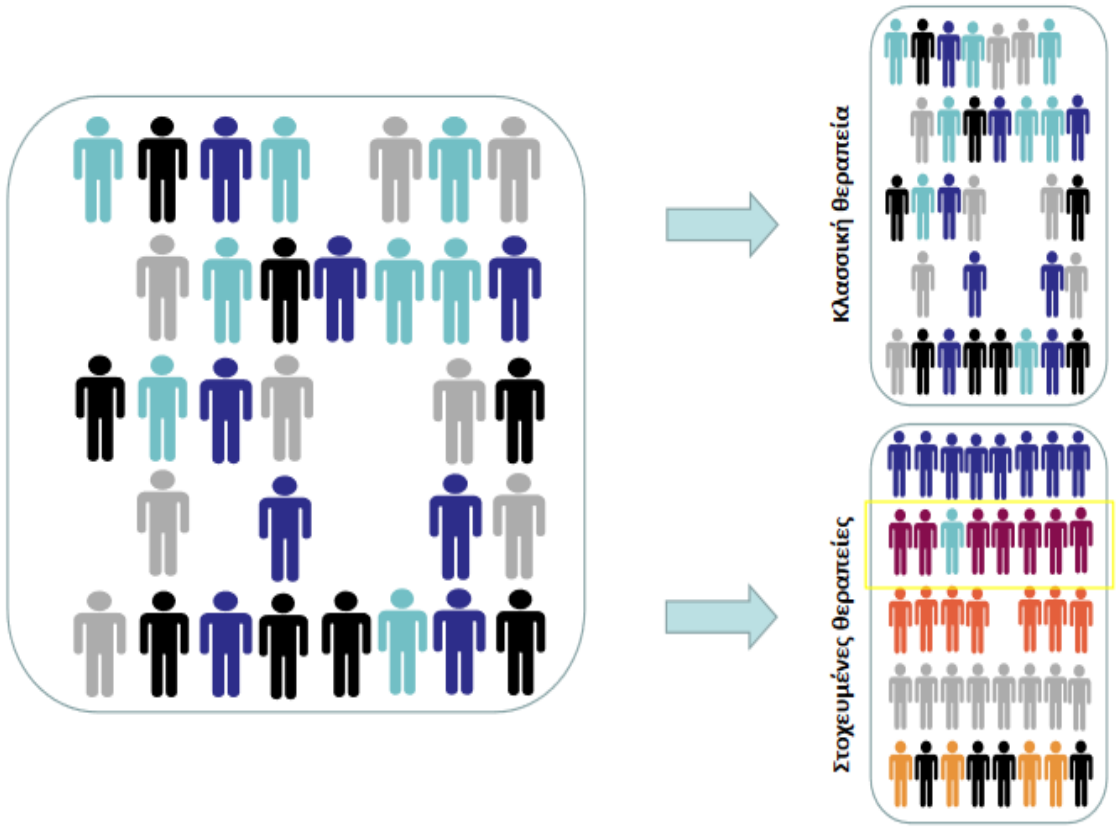
Aspects to consider for optimization of care

3 dimensions of clinical involvement



Del Galdo et al, Lancet Rheumatol. 2020;2:e173-e184

Precision Medicine



- Not all pts with a chronic disease have the “same disease”
- Use of biomarkers (soluble markers, histology, gene expression…) to identify patient subgroups that are more likely to respond to a specific treatment

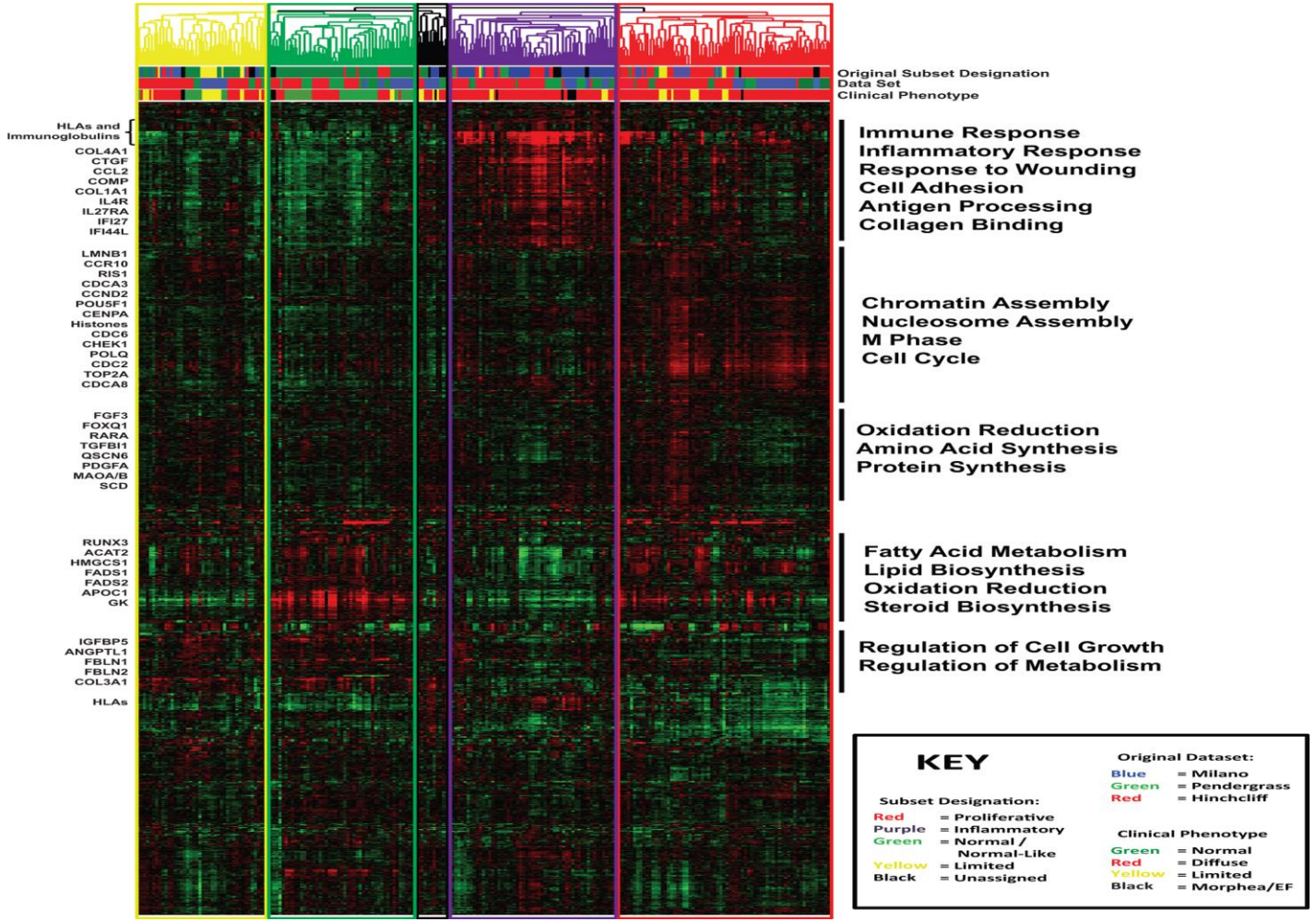
PLOS ONE

Experimentally-Derived Fibroblast Gene Signatures Identify Molecular Pathways Associated with Distinct Subsets of Systemic Sclerosis Patients in Three Independent Cohorts

Michael E. Johnson, J. Matthew Mahoney, Jaclyn Taroni, Jennifer L. Sargent, Eleni Marmarelis, Ming-Ru Wu, John Varga, Monique E. Hinchcliff, Michael L. Whitfield

- Not all patients with SSc have the same skin gene expression

- 4 different signatures in scleroderma skin
  - Fibroproliferative
  - Inflammatory
  - Limited
  - Normal-like

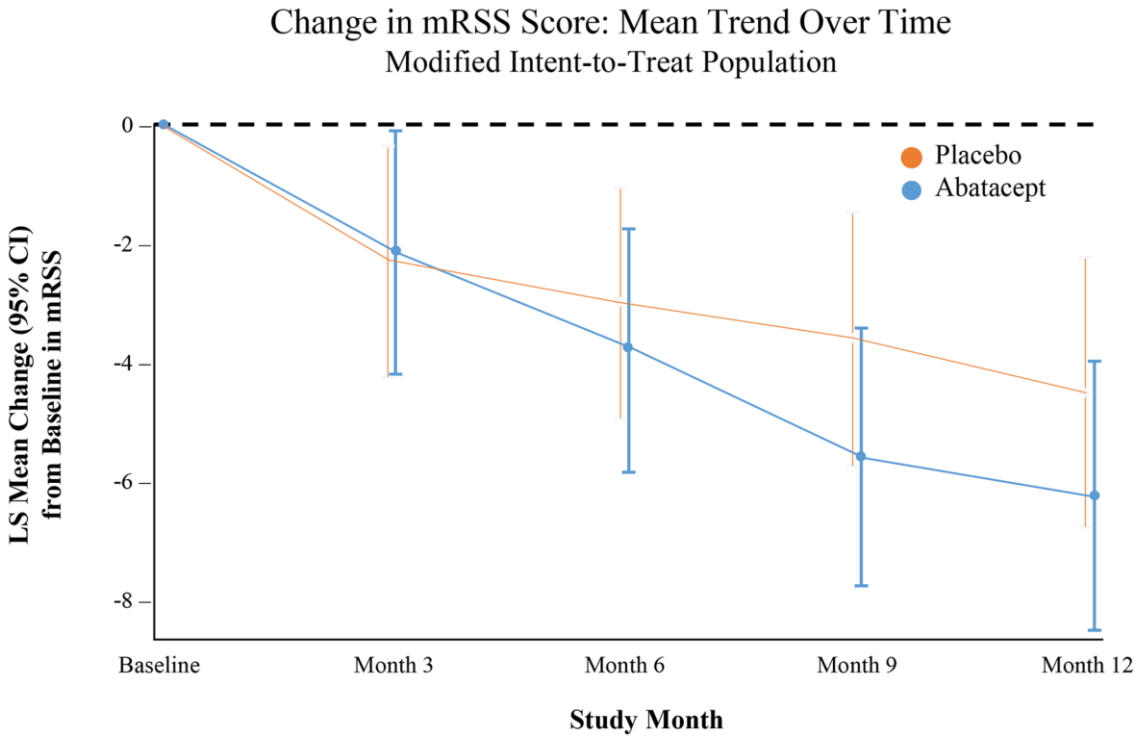


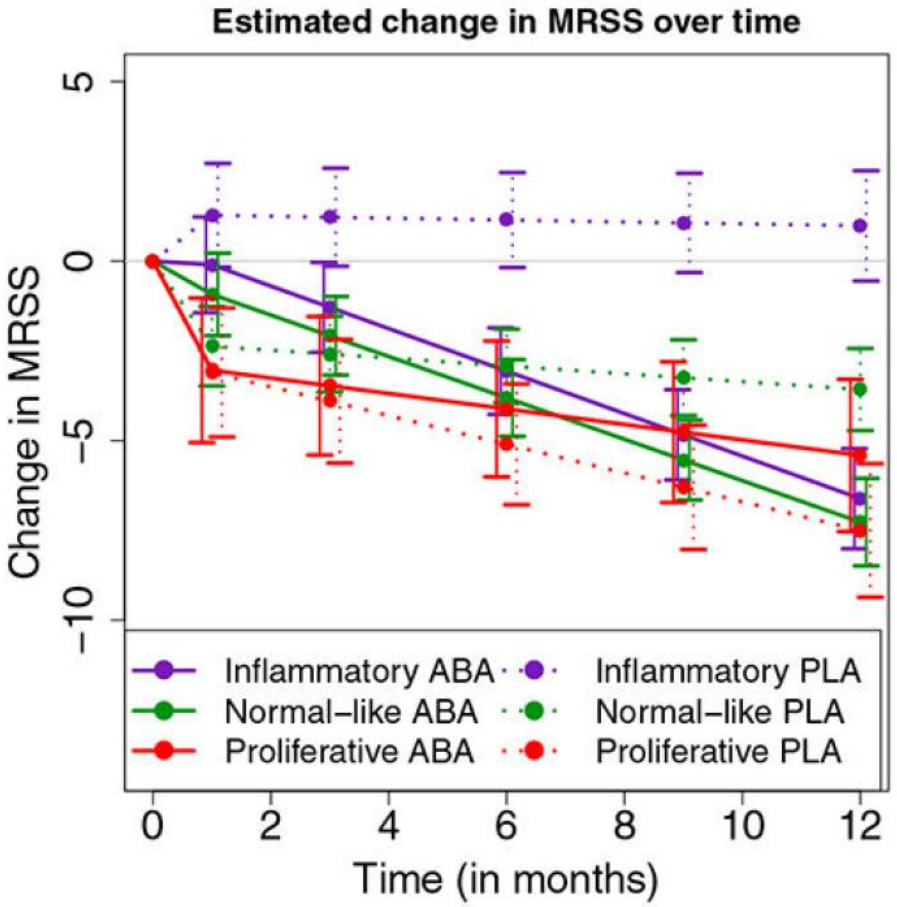
Johnson M, et a PLoS One 2015;10(1):e011401 l

The story of a failed clinical trial…..

Published in final edited form as:
Arthritis Rheumatol. 2020 January ; 72(1): 125–136. doi:10.1002/art.41055.

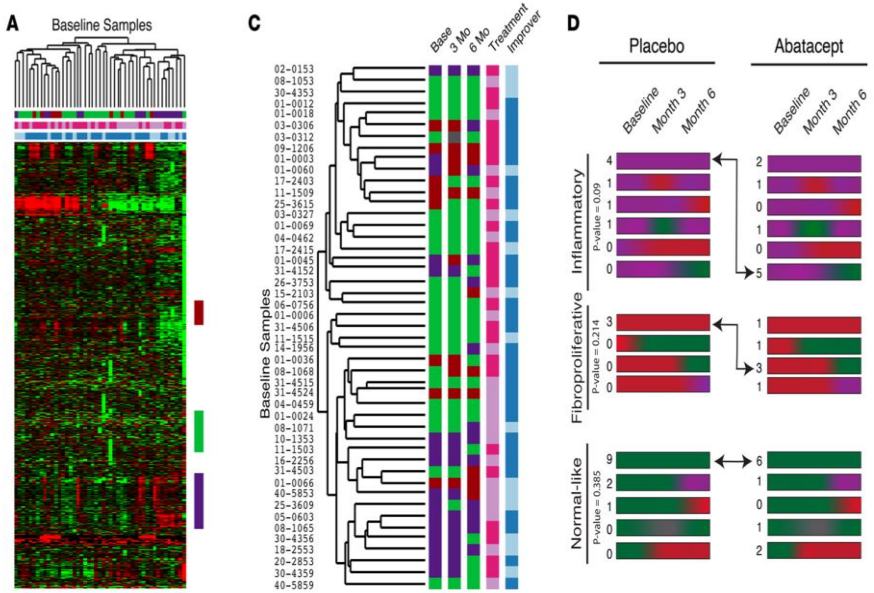
Abatacept in Early Diffuse Cutaneous Systemic Sclerosis – Results of a Phase 2 Investigator-Initiated, Multicenter, Double-Blind Randomized Placebo-Controlled Trial

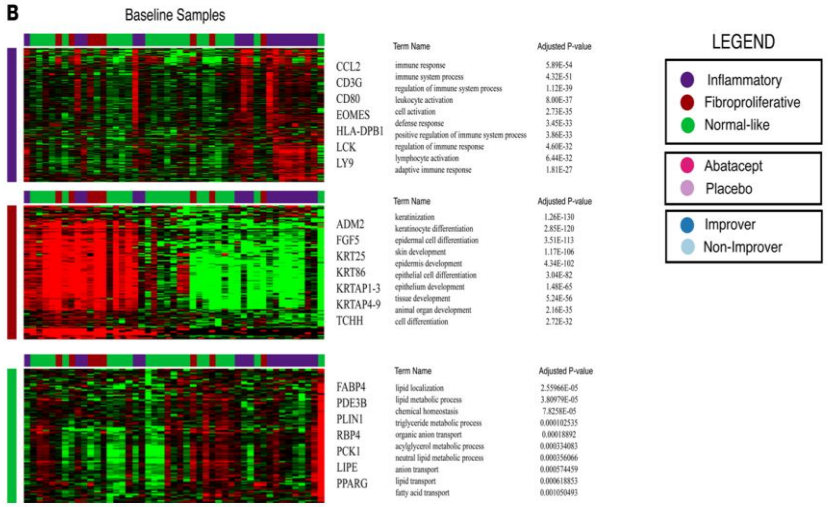




Khanna D et al, Arthritis Rheumatol 2020;72:125-136

Inflammation as a parameter for risk stratification and treatment decisions

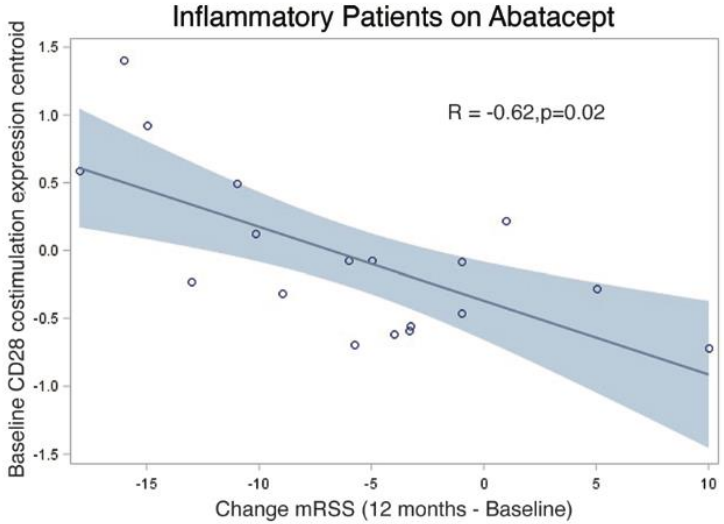




JCI insight

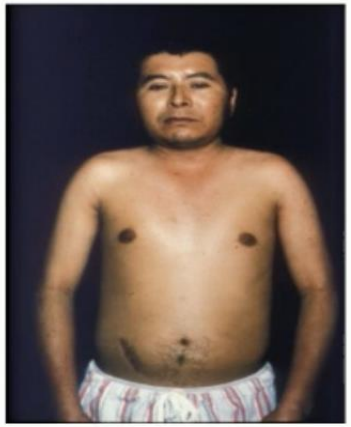
RESEARCH ARTICLE

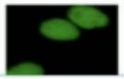
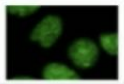
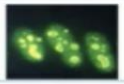
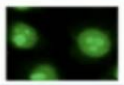
Machine-learning classification identifies patients with early systemic sclerosis as abatacept responders via CD28 pathway modulation

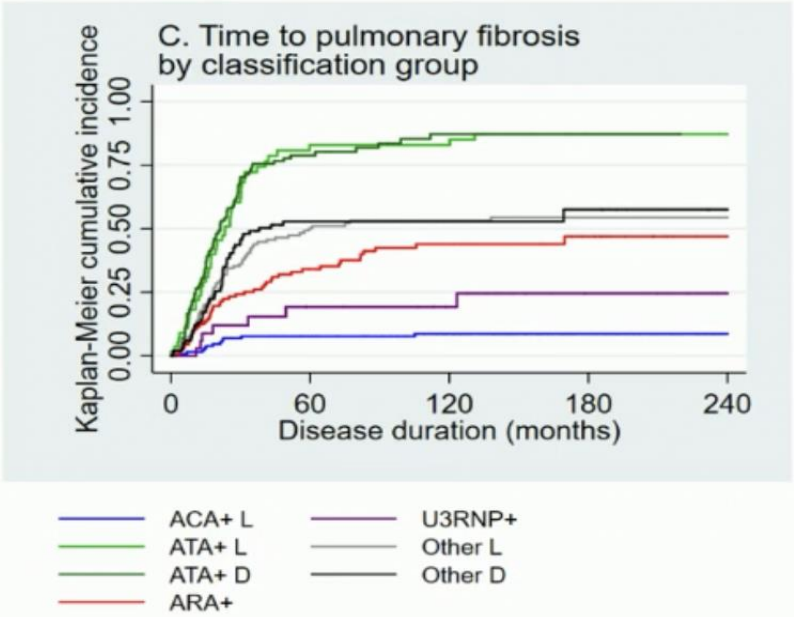


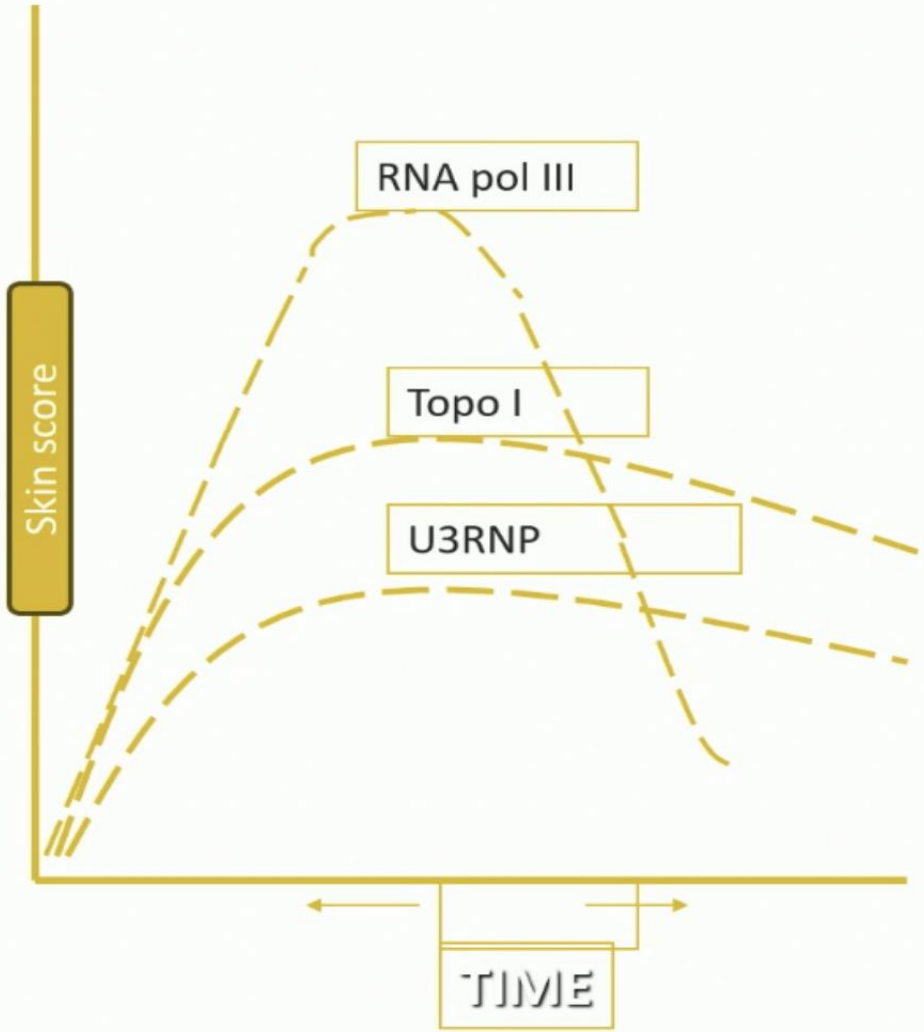
Mehta B et al, JCI Insight 2022;7:e155282

Heterogeneity in outcomes in SSc- Classification based on autoantibodies



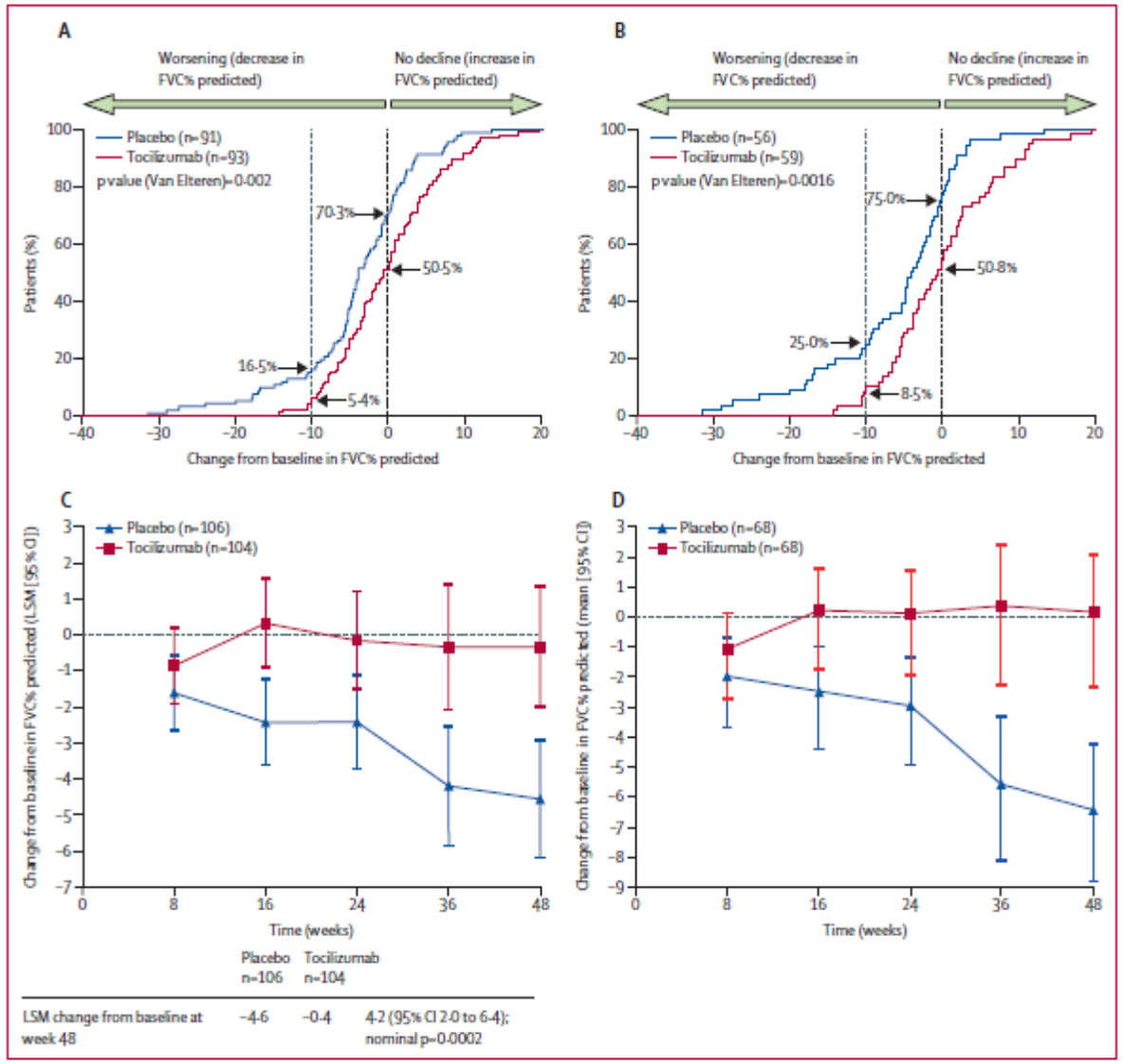
Target antigen	
	Centromere
	Topoisomerase-1 (Scl70)
	RNA polymerase III
	Fibrillarin (U3RNP)
	Pm-Scl





Data derived from: Nihtyanova SI, Denton CP et al Arthritis Rheumatol. 2020;72:465-476.
Figure adapted from: Nihtyanova SI, Denton CP. J Scleroderma Relat Disord 2020;5:6-16.

TOCILIZUMAB IN SSc ILD – The focuSSced Trial



✓Early disease (≤ 5 years duration from first non-Raynaud's phenomenon symptom)

✓Diffuse-progressive skin disease (Scl-70 positive)

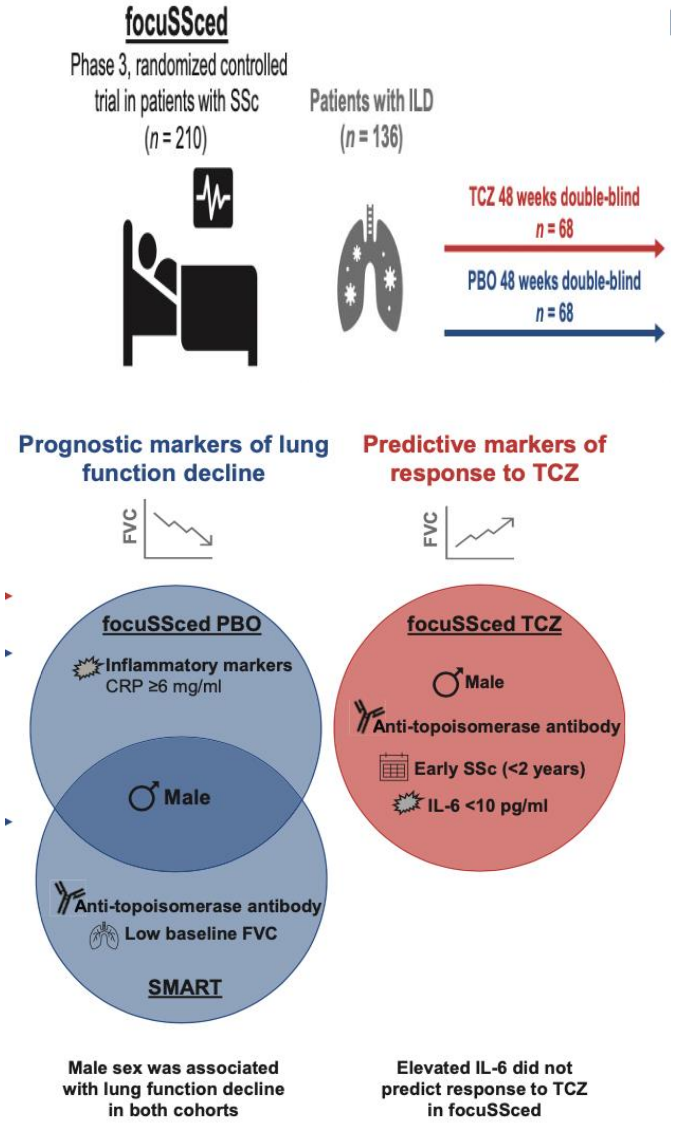
✓↑CRP

✓Mild fibrosis in HRCT (FVC>80%)

Subclinical ILD
↑ risk for progression

Khanna D et al. Am J Respir Crit Care Med 2020;201:A2750

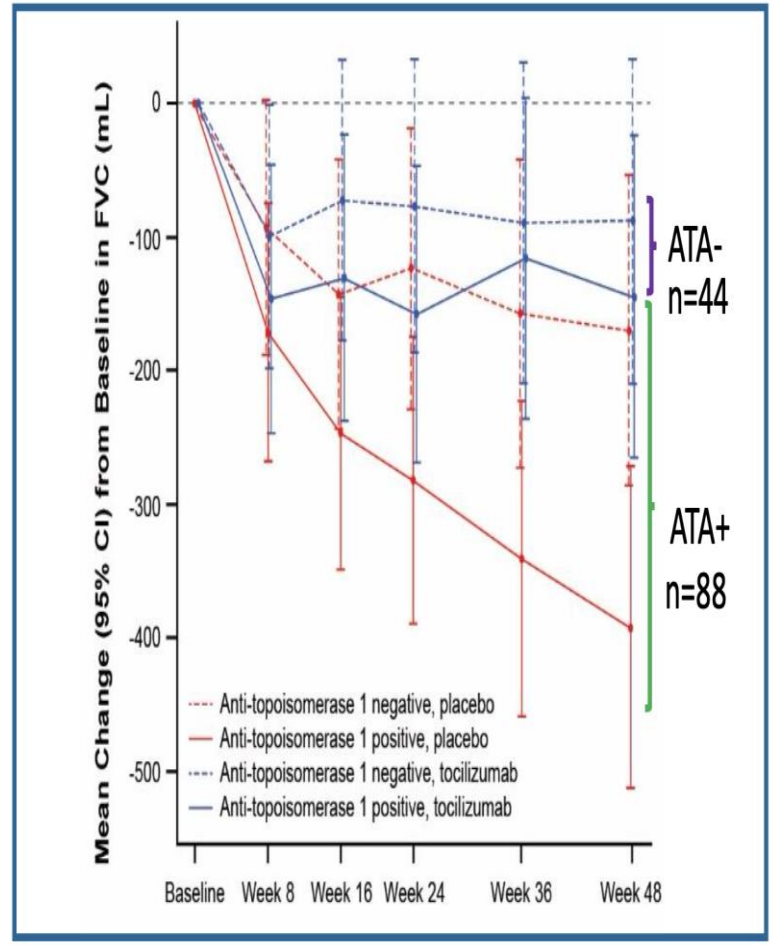
Inflammation and response to TOC



Prognostic markers of lung function decline

FVC

Fixed effects parameter	β	95% CI	P value
Male	1.06	−7.80, 9.92	0.8
Male * week[a]	−0.22	−0.33, −0.11	**0.0001**
IL-6 ≥ 10 pg/mL	−1.45	−8.93, 6.02	0.7
IL6 ≥ 10 pg/mL* week[a]	−0.03	−0.12, 0.07	0.6
CRP ≥ 6 mg/mL	−9.77	−16.67, −2.86	**0.006**
CRP ≥ 6 mg/mL* week[a]	−0.08	−0.17, 0.02	0.1
High IL-6 receptor level	1.59	−5.47, 8.66	0.7
High IL-6 receptor level * week[a]	0.02	−0.07, 0.11	0.7
Platelets > 330 × 10^9/l	2.11	−5.71, 9.94	0.6
Platelets > 330 × 10^9/l * week[a]	−0.10	−0.20, 0.003	0.06
ATA positive	−7.22	−14.92, 0.48	0.07
ATA positive * week[a]	−0.07	−0.17, 0.03	0.2
Age >65 years	1.36	−9.60, 12.31	0.8
Age >65 years * week[a]	0.05	−0.10, 0.19	0.5
Disease duration >2 years	7.11	−0.11, 14.33	0.05
Disease duration >2 years * week[a]	0.09	−0.001, 0.18	0.05



Ghurman A, et al, Rheumatology 2024;63:472–481

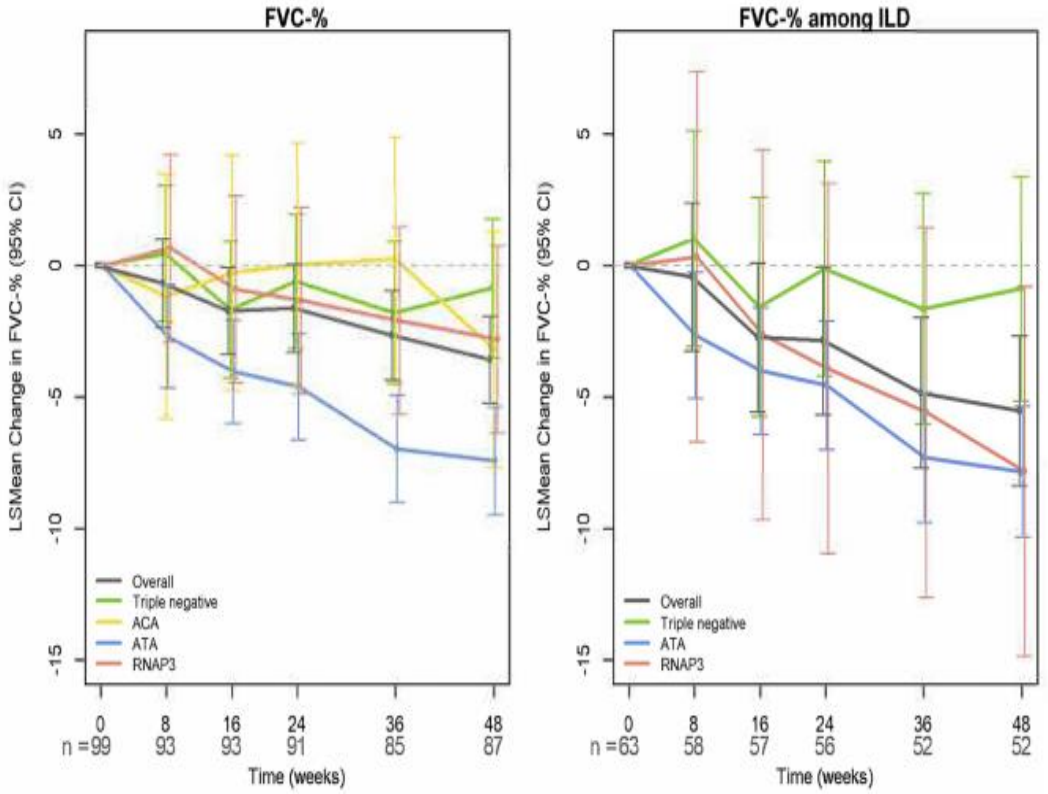
BRIEF REPORT

Impact of Scleroderma-Associated Autoantibodies on Clinical Outcome Assessments: Post Hoc Analysis From a Randomised, Double-blind, Placebo-controlled, Phase 3 Trial of Tocilizumab in Scleroderma

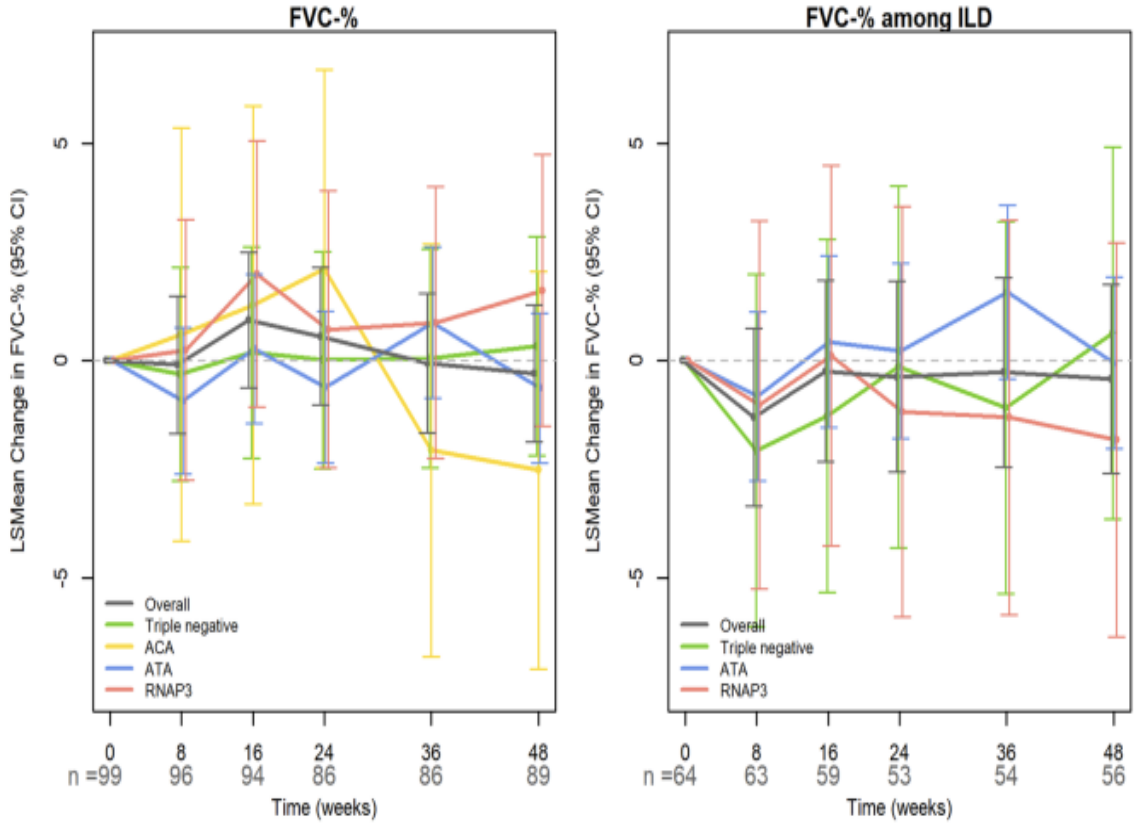
ACR open rheumatology
AN OFFICIAL JOURNAL OF THE American College of Rheumatology

Basmah Al Dulaijan,[1] Suiyuan Huang,[1] Celia J. F. Lin,[2] Christopher P. Denton,[3] and Dinesh Khanna[1]

Placebo



Tocilizumab



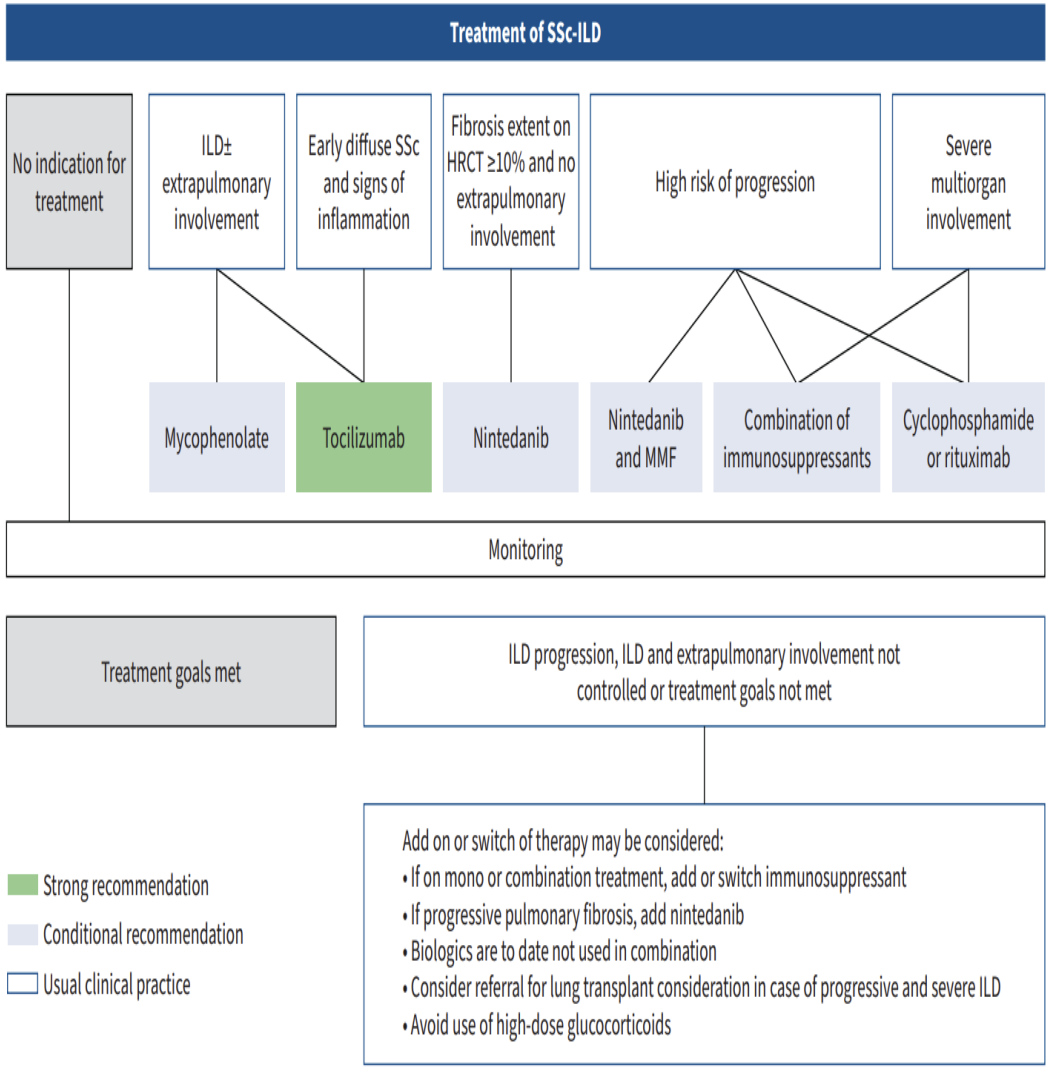
EUROPEAN RESPIRATORY JOURNAL
ERS OFFICIAL DOCUMENTS
K.M. ANTONIOU ET AL.

ERS/EULAR clinical practice guidelines for connective tissue disease-associated interstitial lung disease

Developed by the task force for connective tissue disease-associated interstitial lung disease of the European Respiratory Society (ERS) and the European Alliance of Associations for Rheumatology (EULAR)

Endorsed by the European Reference Network on rare respiratory diseases (ERN-LUNG)

Katerina M. Antoniou[1,36], Oliver Distler[2,36], Ana-Maria Gheorghiu[3], Catharina C. Moor[4], Jens Vikse[5,6,7], Nikoleta Bizymi[1], Ilaria Galetti[8], Graham Brown[9,†], Elena Bargagli[10], Yannick Allanore[11], Tamera J. Corte[12], Philippe Dieudé[13], Vincent Cottin[14], Benjamin A. Fisher[15,16], Aurelie Fabre[17,18], Jon T. Giles[19], Michael Kreuter[20], Ingrid E. Lundberg[21,22], Venerino Poletti[23], Britta Maurer[24], Elisabetta A. Renzoni[25], Ulf Müller-Ladner[26], Mary E. Strek[27], Nicola Sverzellati[28], Paul Studenic[21,29], Jibril Mohammed[30], Blin Nagavci[31], Tanja Stamm[32], Thomy Tonia[33], Bruno Crestani[34,36] and Anna-Maria Hoffmann-Vold[2,35,36]



Eur Respir J. 2025 Sep 11:2500896./ Ann Rheum Dis. 2025 Sep 3:S0003-4967(25)04320-1

Rheumatology, 2024, **63**, 2956–2975
https://doi.org/10.1093/rheumatology/keae394
Advance access publication 11 September 2024
BSR Guidelines

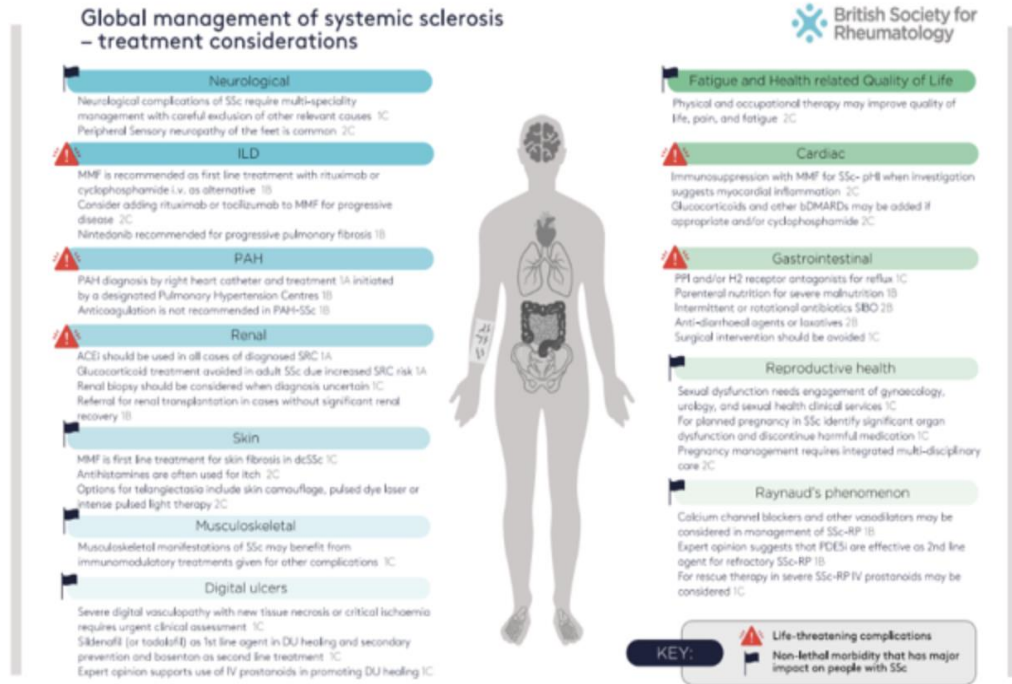
British Society for Rheumatology RHEUMATOLOGY OXFORD

•DOI: 10.1093/rheumatology/keae394

BSR Guidelines

The 2024 British Society for Rheumatology guideline for management of systemic sclerosis

Christopher P. Denton[1,*], Enrico De Lorenzis[2], Elen Roblin[3], Nina Goldman[1], Begonya Alcacer-Pitarch[2], Emma Blamont[4], Maya H. Buch[5], Maresa Carulli[6], Caroline Cotton[7], Francesco Del Galdo[2], Emma Derrett-Smith[8], Karen Douglas[9], Sue Farrington[4], Kim Fligelstone[3], Luke Gompels[10], Bridget Griffiths[11], Ariane Herrick[5], Michael Hughes[5], Clare Pain[12], Georgina Pantano[13], John D. Pauling[14], Athiveeraramapandian Prabu[8], Nuala O'Donoghue[15], Elisabetta A. Renzoni[16], Jeremy Royle[17], Muditha Samaranayaka[18], Julia Spierings[19], Aoife Tynan[3], Louise Warburton[20], Voon H. Ong[1]



i) Consider tocilizumab as first-line treatment in early dcSSc with raised inflammatory markers and ATA positivity, independent of the extent of ILD on CT (1A, 92%).

EUROPEAN RESPIRATORY JOURNAL
ERS OFFICIAL DOCUMENTS
K.M. ANTONIOU ET AL.

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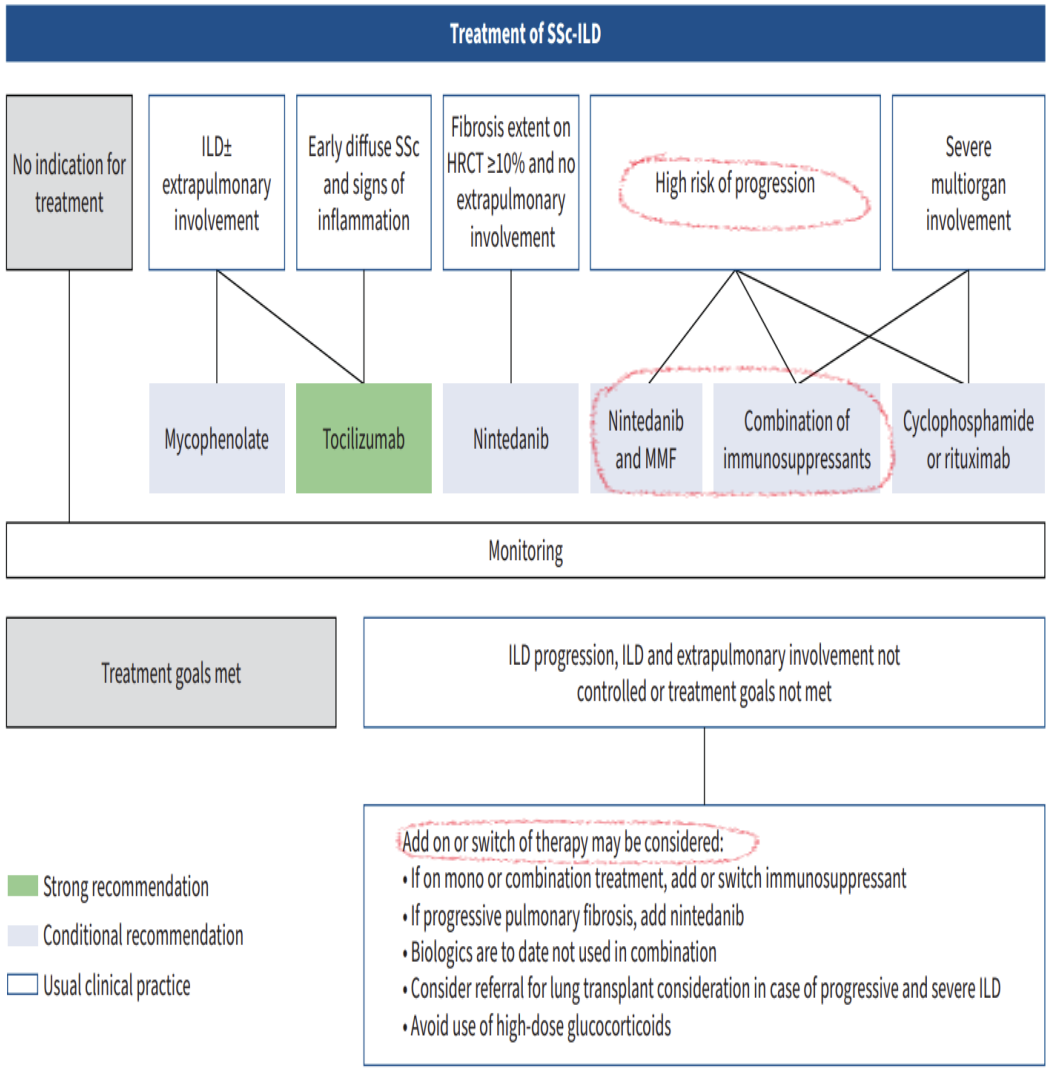
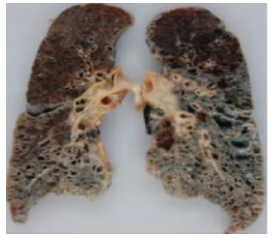
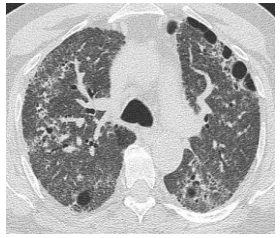
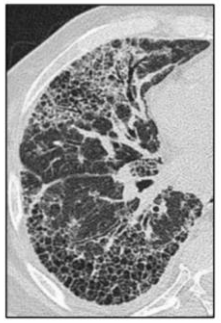
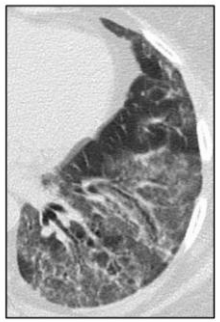


Recommendation

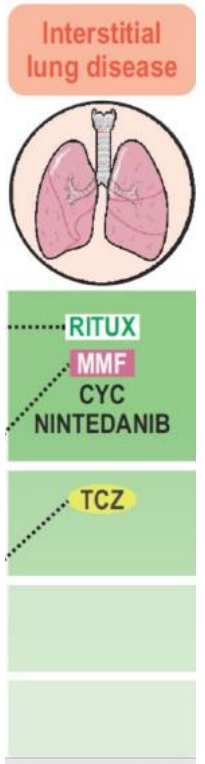
for SSc-ILD

Recommendation	LoE	SoR	LoA (SD)	% LoA>8
MMF (1A), cyclophosphamide (1A) or rituximab (1A) should be considered for the treatment of SSc-ILD*	1a	A	8.1 (2.8)	88
Nintedanib should be considered alone or in combination with MMF for the treatment of SSc-ILD*	1a	A	8.5 (2.5)	84
Tocilizumab should be considered for the treatment of SSc-ILD*	1b	B	7.8 (2.8)	76

new

- MMF – results for SLSII
- CYP – oral in SLS, iv in RECITAL
- RTX – RECITAL study (RTX vs ivCYP), DESIRES study - approved in Japan for SSc-ILD
- TCZ – FDA approved for SSc-ILD

- Nintedanib – SENSCIS and INBUILD trials
  - Alone or in combi with MMF



Recommendation

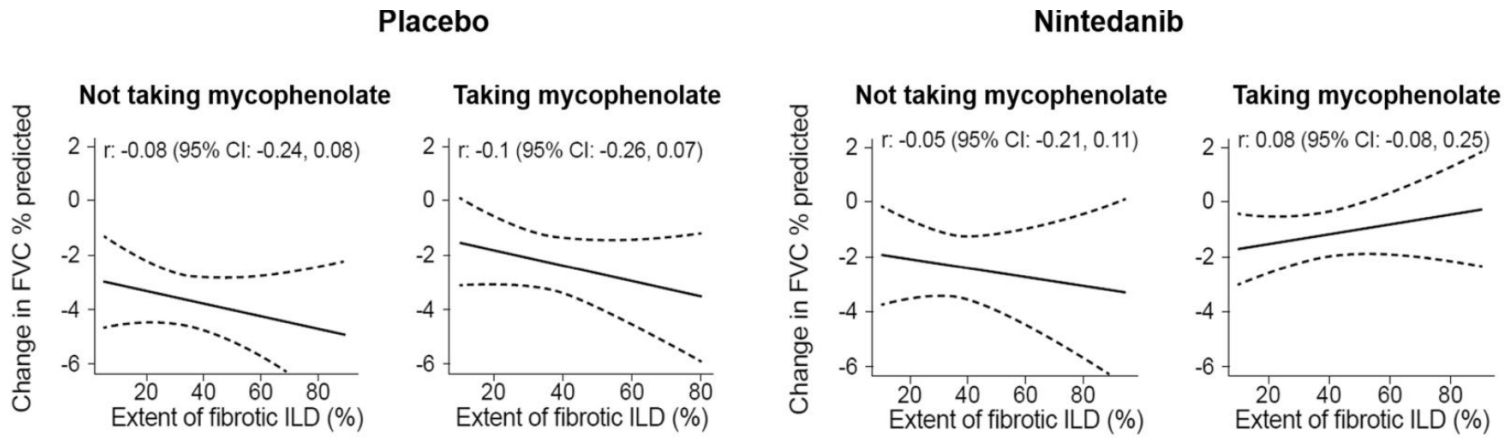
EULAR recommendations for the treatment of systemic sclerosis: 2023 update

Francesco Del Galdo [1,2] Alain Lescoat [3] Philip G Conaghan [1,2] Eugenia Bertoldo,[4] Jelena Čolić,[5] Tânia Santiago [6] Yossra A Suliman,[7,8] Marco Matucci-Cerinic [9] Armando Gabrielli,[10] Oliver Distler [11] Anna-Maria Hoffmann-Vold [12] Ivan Castellví [13] Alexandra Balbir-Gurman,[14] Madelon Vonk [15] Lidia Ananyeva,[16] Simona Rednic,[17] Anna Tarasova,[18] Pedrag Ostojic,[19] Vladimira Boyadzhieva,[20] Khadija El Aoufy,[21] Sue Farrington,[22,23] Ilaria Galetti,[23] Christopher P Denton [24] Otylia Kowal-Bielecka,[25] Ulf Mueller-Ladner,[26] Yannick Allanore [27]

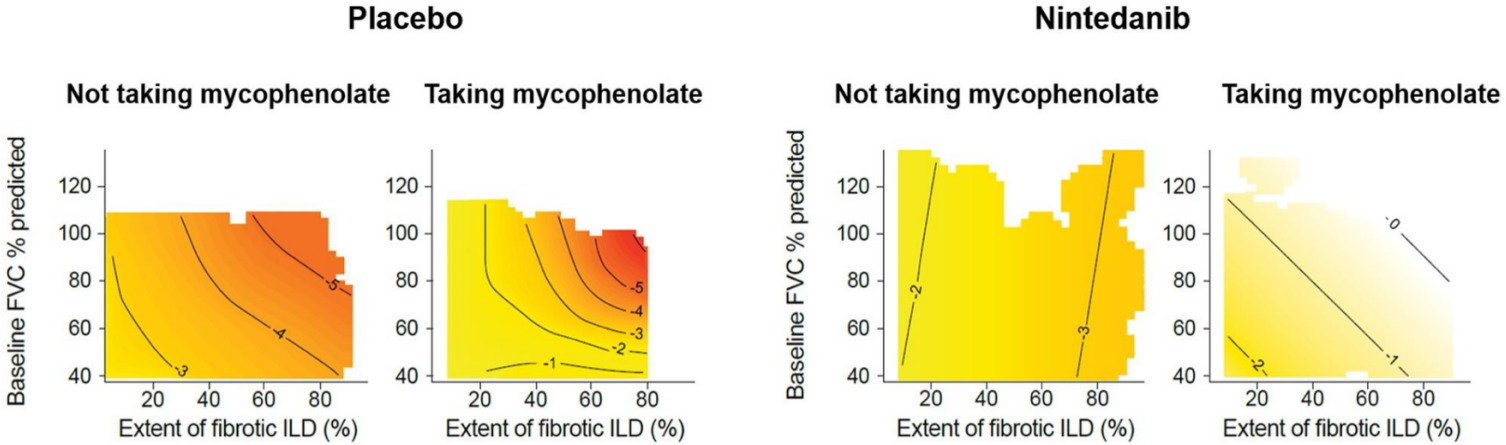
Del Galdo F, *et al*. *Ann Rheum Dis* 2024;**0**:1–12. doi:10.1136/ard-2024-226430

RHEUMATOLOGY

Extent of fibrosis and lung function decline in patients with systemic sclerosis and interstitial lung disease: data from the SENSCIS trial

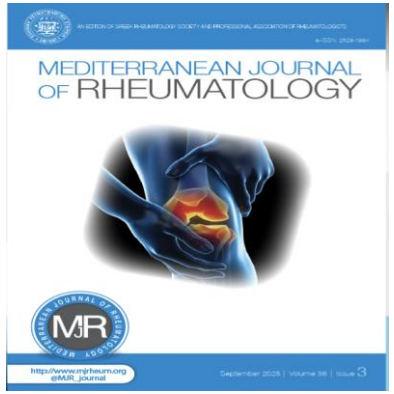


Associations between extent of fibrotic ILD on HRCT at baseline and change in FVC at week 52 in subgroups by mycophenolate use at baseline



Contour plots of change in FVC at week 52 by extent of fibrotic ILD on HRCT and FVC at baseline. Darker shading indicates greater decline in FVC % predicted at week 52.

Denton CP et al, Rheumatology. 2023 May; 62(5): 1870–1876

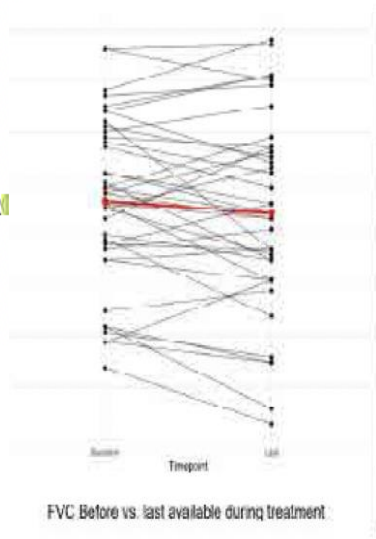


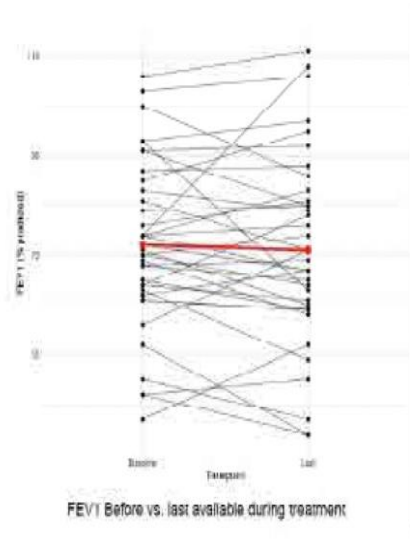
Treatment Response and Safety Profile of Nintedanib in Connective Tissue Disease-Associated Interstitial Lung Disease: A Retrospective Observational Study

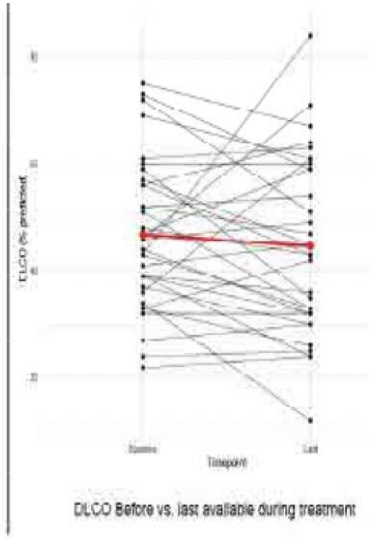
Arriana Gkouvi[1], Maria Boutel[2], Nikoleta Zioga[1], Eleni Pagkopoulou[2], Maria Mytilinaiou[2], Christina Rampiadou[3], George A. Margaritopoulos[4], Dimitrios P. Bogdanos[1], Theodoros Dimitroulas[2], Theodora Simopoulou[1]

Age	Mean ± SD [Median (IQR)]	60.1 ± 11.8 [62 (12)]
Gender	Male % (n)	28.3% (17)
Disease type	SSc % (n)	50.0% (30)
	RA % (n)	21.7% (13)
	IIM % (n)	13.3% (8)
	IPAF % (n)	5.0% (3)
	MCTD/UCTD % (n)	8.3% (5)
	JIA % (n)	1.7% (1)
CTD-ILD duration (yrs)	Mean ± SD [Median (IQR)]	6.7 ± 4.2 [6 (5)]

Regimen	n	%
PRED	36	60
MMF	29	48
RTX	21	35
TOC	8	13,3
MTX	5	8,3
LEF/AZA	3/1	5/1,5


FVC Before vs. last available during treatment

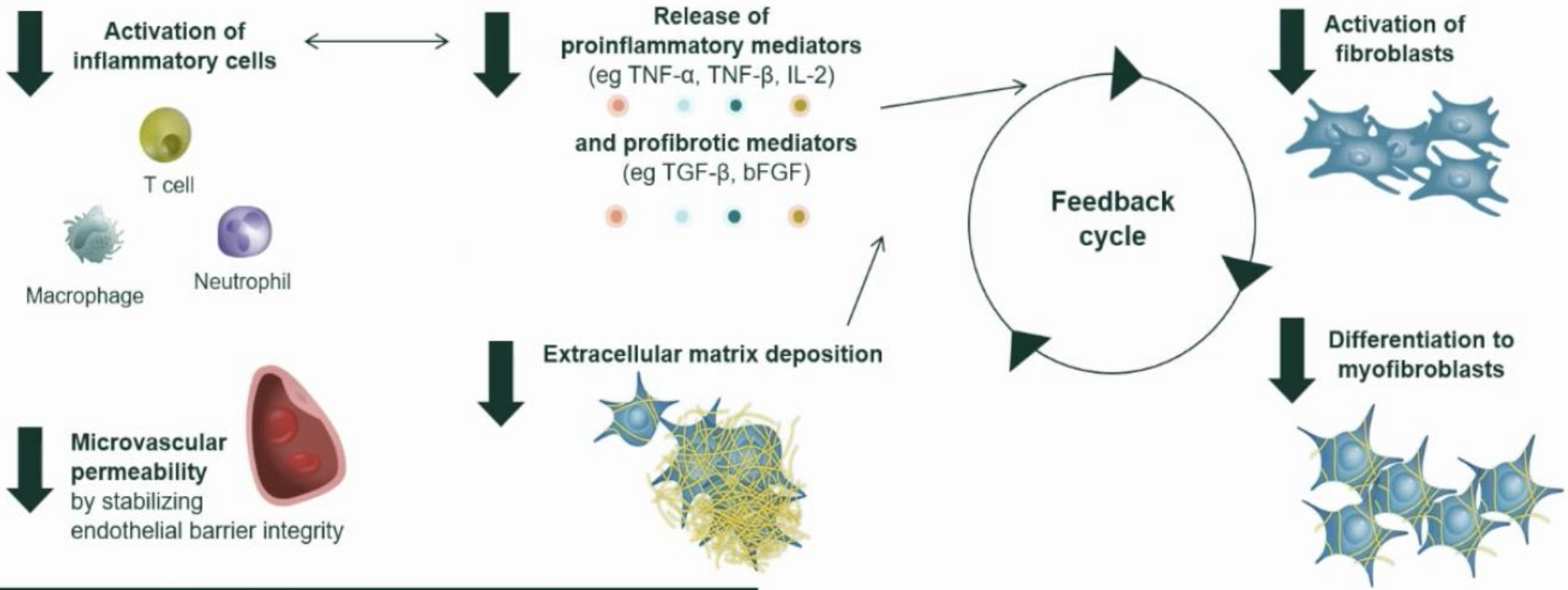

FEV1 Before vs. last available during treatment


DLCO Before vs. last available during treatment

Variable	Characteristics	Value	N	p-value (95% CIs)
FVC	Baseline FVC	66.5 ± 16.4†	39	0.090#(-5.33, 0.41)
	FVC after	64.1 ± 19.0†		
	% change in FVC	-4.2 ± 15.0%†		
DLCO	Baseline DLCO	46.8 ± 14.0†	33	0.139$
	DLCO after	44.6 ± 16.6†		
	% change in DLCO	-2.9 ± 31.9% [-9.6 (30.3)%]††		
FEV1	Baseline FEV1	72.1 ± 16.9†	37	0.398$
	FEV1 after	70.9 ± 19.3†		
	% change in FEV1	-1.2 ± 16.9%†		
FVC/DLCO	Baseline FVC/DLCO	1.6 ± 0.8 [1.5 (0.5)]††	31	0.518$
	FVC/DLCO after	1.4 ± 0.9 [1.4 (0.7)]††		

Gouvi A at al, Mediterr J Rheumatol 2025;36(3):370-379

Nerandomilast is a preferential inhibitor of PDE4B with antifibrotic and immunomodulatory properties and effects on vascular dysfunction in pre-clinical studies



Low emetic potential in *Suncus murinus*

Lower mean number of emetic events with nerandomilast than roflumilast

bFGF, basic fibroblast growth factor. IL-2, interleukin-2. PDE4B, phosphodiesterase 4B. PDGF, platelet-derived growth factor. TGF-β, transforming growth factor-β. TNF-α, tumor necrosis factor-α. TNF-β, tumor necrosis factor-β. VEGF, vascular endothelial growth factor.

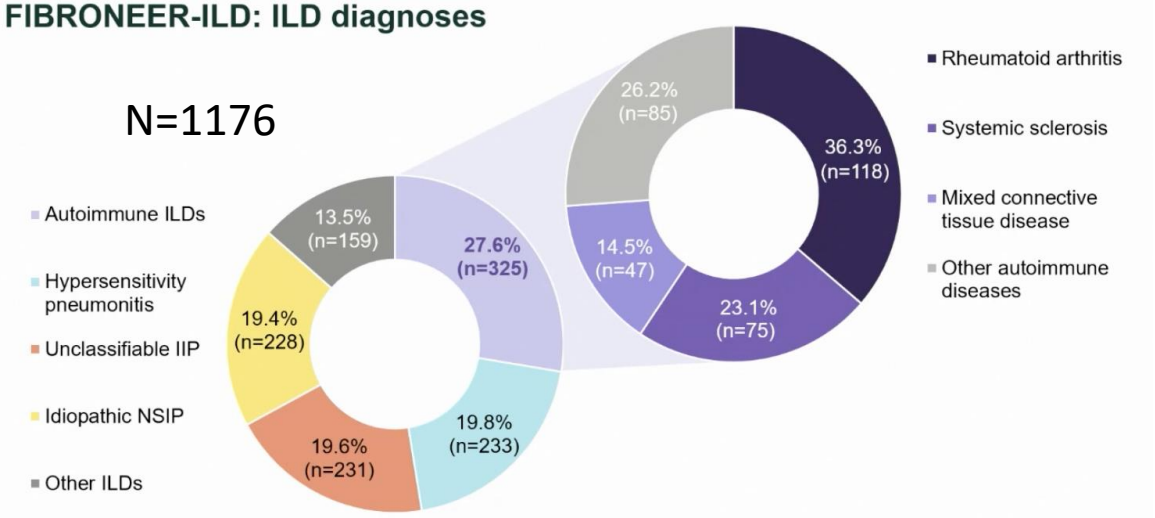
Herrmann FE et al. Front Pharmacol 2022:13:838449.

The NEW ENGLAND JOURNAL of MEDICINE

Nerandomilast in Patients with Progressive Pulmonary Fibrosis

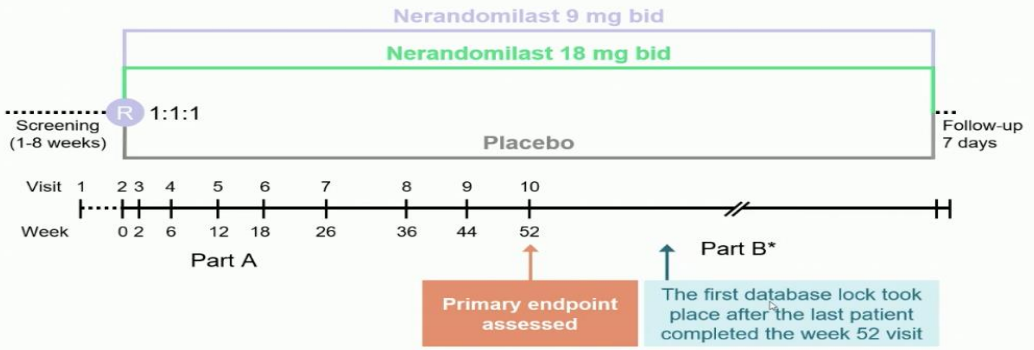
Toby M. Maher, M.D.,[1,2] Shervin Assassi, M.D.,[3] Arata Azuma, M.D.,[4,5] Vincent Cottin, M.D.,[6] Anna-Maria Hoffmann-Vold, M.D.,[7,8] Michael Kreuter, M.D.,[9,10] Justin M. Oldham, M.D.,[11] Luca Richeldi, M.D.,[12] Claudia Valenzuela, M.D.,[13] Marlies S. Wijsenbeek, M.D.,[14] Emmanuelle Clerisme-Beaty, M.D.,[15] Carl Coeck, M.D.,[16] Hui Gu, Ph.D.,[17] Ivana Ritter, M.D.,[15] Arno Schlosser, M.Sc.,[18] Susanne Stowasser, M.D.,[15] Florian Voss, Ph.D.,[19] Gerrit Weimann, M.D.,[15] Donald F. Zoz, M.D.,[20] and Fernando J. Martinez, M.D.,[21] for the FIBRONEER-ILD Trial Investigators*

FIBRONEER-ILD: ILD diagnoses



Autoimmune ILDs: rheumatoid arthritis-associated ILD, systemic sclerosis-associated ILD, mixed connective tissue disease-associated ILD and selected terms within 'Other fibrosing ILD'.
Other ILDs: sarcoidosis-ILD, exposure-related ILDs and selected terms within 'Other fibrosing ILD'.

Trial design



Key exclusion criteria

Respiratory
- Pre-bronchodilator FEV_1/FVC <0.7
- Acute exacerbation of ILD within 3 months prior to screening

Psychiatric
- Suicidal behavior in prior 2 years or suicidal ideation (type 4 or 5 on C-SSRS) in 3 months prior to or at screening or randomisation
- Acute or chronic severe depression (HADS subscore >14) at screening or randomisation

Liver and kidney function
- AST or ALT >2.5× or total bilirubin >1.5× upper limit of normal
- eGFR ≤30 mL/min/1.73m²
- Child-Pugh A, B, or C hepatic impairment

Therapies
- Pirfenidone, cyclophosphamide, tocilizumab, mycophenolate, rituximab, or prednisone >15 mg/day or equivalent

Use of immunosuppressant therapy at baseline in overall trial population

	Placebo (n=392)	Nerandomilast 9 mg bid (n=393)	Nerandomilast 18 mg bid (n=391)
Any immunosuppressant therapy[1*]	97 (24.7)	97 (24.7)	89 (22.8)
Azathioprine[2]	32 (8.2)	35 (8.9)	19 (4.9)
Methotrexate[2]	14 (3.6)	14 (3.6)	25 (6.4)
Hydroxychloroquine sulfate[2]	20 (5.1)	13 (3.3)	10 (2.6)
Hydroxychloroquine[2]	8 (2.0)	14 (3.6)	11 (2.8)
Tacrolimus[2]	10 (2.6)	10 (2.5)	8 (2.0)
Ciclosporin[2]	7 (1.8)	10 (2.5)	4 (1.0)
Leflunomide[2]	7 (1.8)	6 (1.5)	8 (2.0)
Abatacept[2]	1 (0.3)	4 (1.0)	7 (1.8)
Colchicine[2]	4 (1.0)	2 (0.5)	0 (0)
Methotrexate sodium[2]	1 (0.3)	1 (0.3)	4 (1.0)
Iguratimod[2]	0 (0)	3 (0.8)	2 (0.5)

Maher TM eta al, N Engl J Med. 2025 Jun 12;392(22):2203-2214.

The NEW ENGLAND JOURNAL of MEDICINE

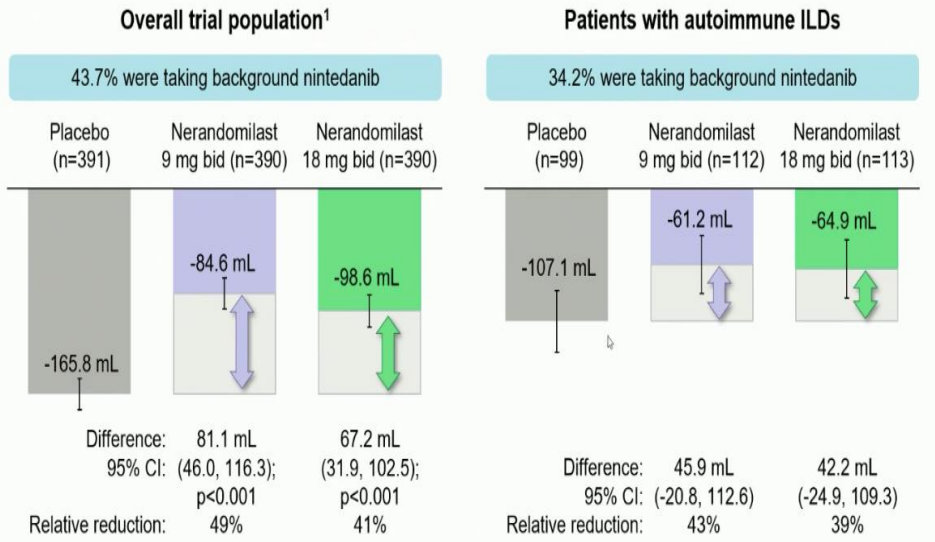
Nerandomilast in Patients with Progressive Pulmonary Fibrosis

Toby M. Maher, M.D.,[1,2] Shervin Assassi, M.D.,[3] Arata Azuma, M.D.,[4,5] Vincent Cottin, M.D.,[6] Anna-Maria Hoffmann-Vold, M.D.,[7,8] Michael Kreuter, M.D.,[9,10] Justin M. Oldham, M.D.,[11] Luca Richeldi, M.D.,[12] Claudia Valenzuela, M.D.,[13] Marlies S. Wijsenbeek, M.D.,[14] Emmanuelle Clerisme-Beaty, M.D.,[15] Carl Coeck, M.D.,[16] Hui Gu, Ph.D.,[17] Ivana Ritter, M.D.,[15] Arno Schlosser, M.Sc.,[18] Susanne Stowasser, M.D.,[15] Florian Voss, Ph.D.,[19] Gerrit Weimann, M.D.,[15] Donald F. Zoz, M.D.,[20] and Fernando J. Martinez, M.D.,[21] for the FIBRONEER-ILD Trial Investigators*

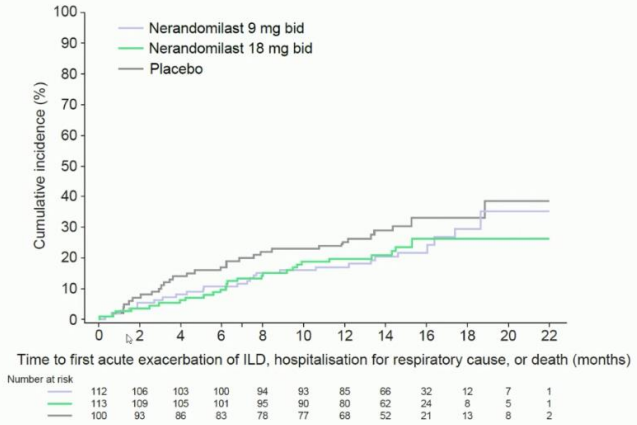
55% were taking background immunosuppressive therapy

34.2% were taking background nintedanib

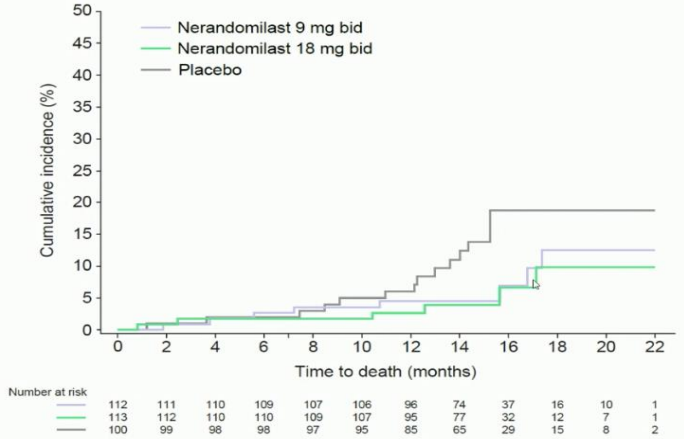
Changes in FVC (mL) at week 52



Time to acute exacerbation of ILD, hospitalisation for respiratory cause, or death in patients with autoimmune ILDs



Time to death in patients with autoimmune ILDs



Maher TM eta al, N Engl J Med. 2025 Jun 12;392(22):2203-2214.

Recommendation

EULAR recommendations for the treatment of systemic sclerosis: 2023 update

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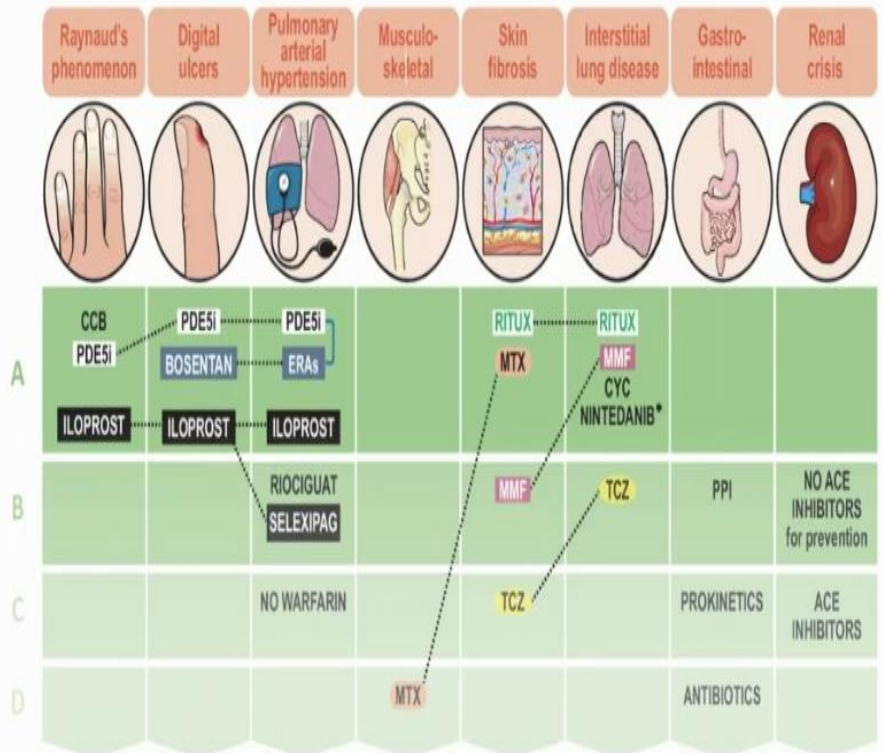
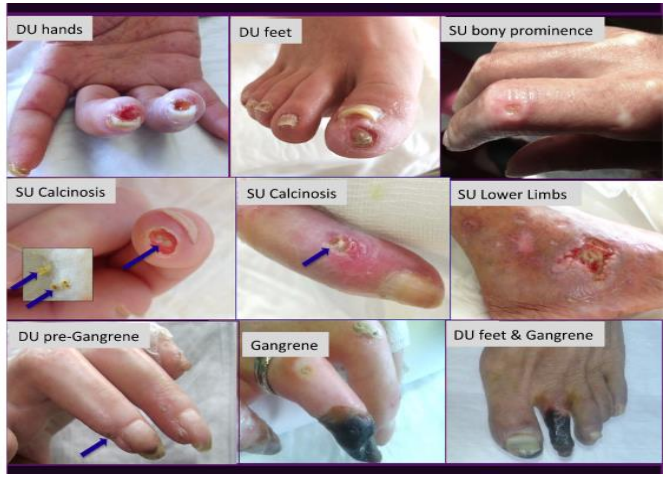
The 2023 EULAR recommendations for the treatment of SSc focused on eight clinical domains

20 recommendations
(16 in 2017)

- 8 disease domains
- First-line and second-line considerations
- Level of evidence (1–5)
- 4 strengths
  - A = should be considered
  - B = can be considered
  - C = may be considered
  - D = expert opinion



Del Galdo F, *et al*. *Ann Rheum Dis* 2024;**0**:1–12. doi:10.1136/ard-2024-226430



Recommendation

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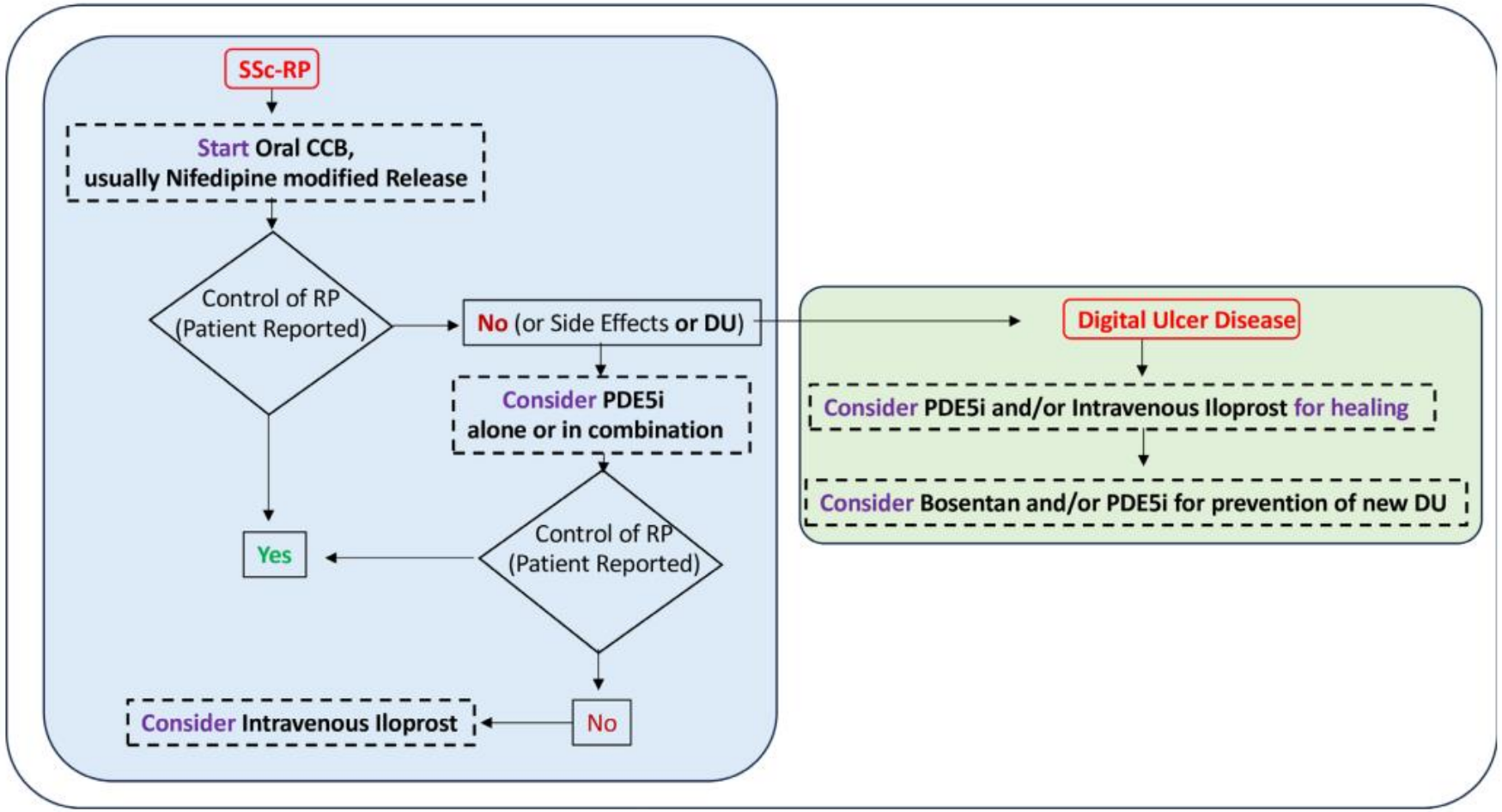
Recommendation

for treatment of Raynaud's phenomenon and (ischaemic) DU disease

Treatment flow chart



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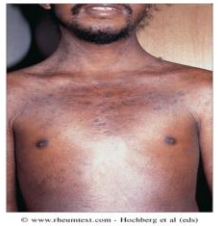
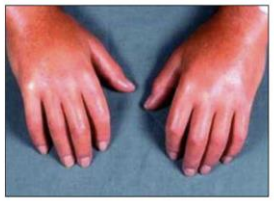
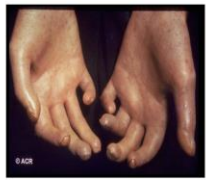
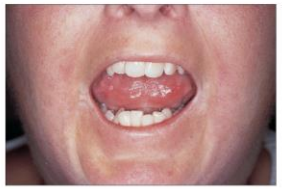








new

Recommendation

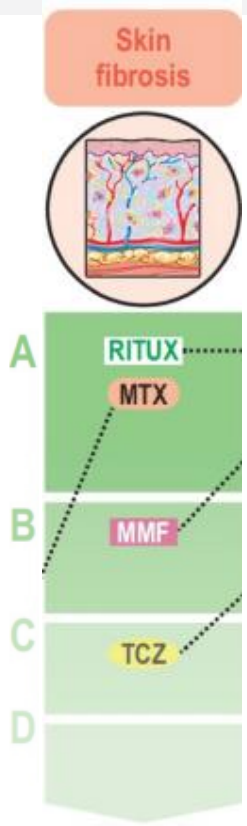
for skin fibrosis

Recommendation	LoE	SoR	LoA (SD)	% LoA>8
Methotrexate (1B), mycophenolate mofetil (MMF) (1B) and/or rituximab (1A) should be considered for treatment of SSc skin fibrosis*	1a-b	A/B	7.6 (3.2)	72
Tocilizumab may be considered for the treatment of skin fibrosis in patients with early, inflammatory dcSSc*	1b	C	7.2 (2.1)	60

Skin

Recommendation, LoE (SoR)

- MTX, 1B; MMF, 1B; and/or RITUX, 1A should be considered for treatment of SSc skin fibrosis (A/B)
- TCZ may be considered for the treatment of skin fibrosis in patients with early, inflammatory dcSSc, 1B (C)



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Del Galdo F, *et al*. *Ann Rheum Dis* 2024;**0**:1–12. doi:10.1136/ard-2024-226430

Clinical science

Efficacy of methylprednisolone in very early systemic sclerosis: results of the 'Hit Hard and Early' randomized controlled trial

Brigit E. Kersten [1,*], Jacqueline M. J. Lemmers [1], Amber Vanhaecke [2], Arthiha Velauthapillai [1], Wieneke M. T. van den Hombergh [1], Frank H. J. van den Hoogen[1], Cornelia H. M. van den Ende[1], Vanessa Smith [2,‡], Madelon C. Vonk[1,‡]

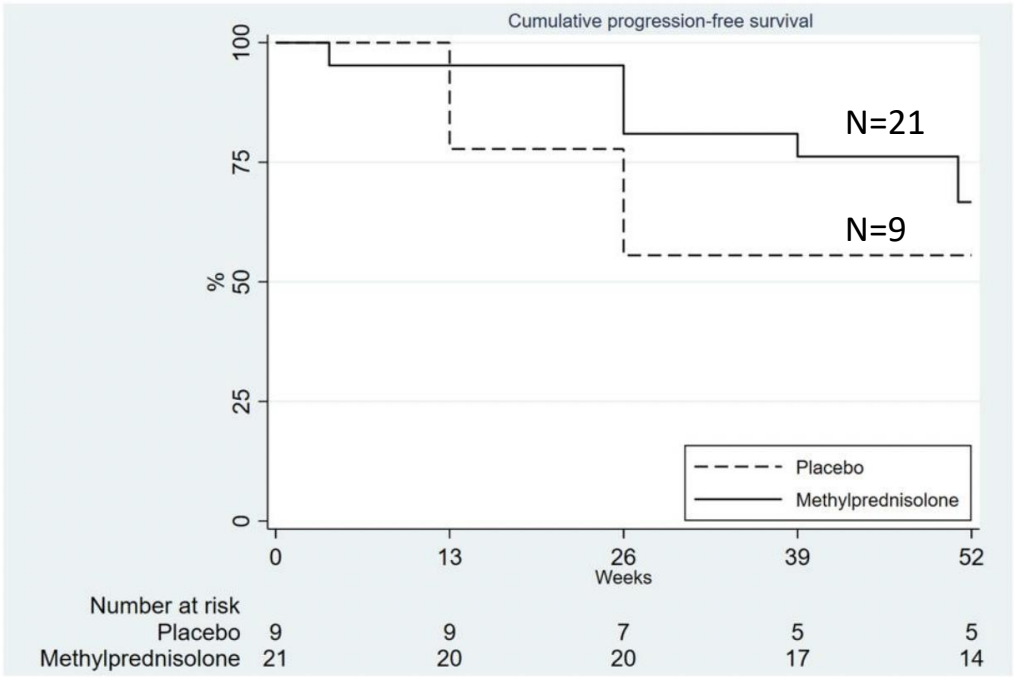
1000mg Solu Medrol x 3 for 3 months
PPi daily
ACE daily

IN

- ✓ age 18 years or older
- ✓ presence of Raynaud's phenomenon
- ✓ positive test for associated auto-antibodies
- ✓ early or active SSc pattern at nailfold capillaroscopy
- ✓ and puffy fingers for < 3 years

OUT

- ✓ any skin or internal organ involvement
- ✓ the presence of interstitial lung disease on HRCT-scan
- ✓ previous treatment for SSc
- ✓ *anti-RNA polymerase III auto-antibodies*



Rheumatology (Oxford).2024,:3;1261–1269

Oral Glucocorticoids for Skin Fibrosis in Early Diffuse Systemic Sclerosis: A Target Trial Emulation Study From the European Scleroderma Trials and Research Group Database

Denis Mongin,[1] Marco Matucci-Cerinic,[2] Ulrich A. Walker,[3] Oliver Distler,[4] Radim Becvar,[5] Elise Siegert,[6] Lidia P. Ananyeva,[7] Vanessa Smith,[8] Juan Jose Alegre-Sancho,[9] Sule Yavuz,[10] Massimiliano Limonta,[11] Gabriela Riemekasten,[12] Elena Rezus,[13] Madelon Vonk,[14] Marie-Elise Truchetet,[15] Francesco Del Galdo,[16] Delphine S. Courvoisier,[1] and Michele Iudici,[1] on behalf of the EUSTAR Collaborators

208 patients (mean age 49 years; 33% male; 59% anti-Scl70), 104 in each group, median prednisone dose of 5 mg/day.

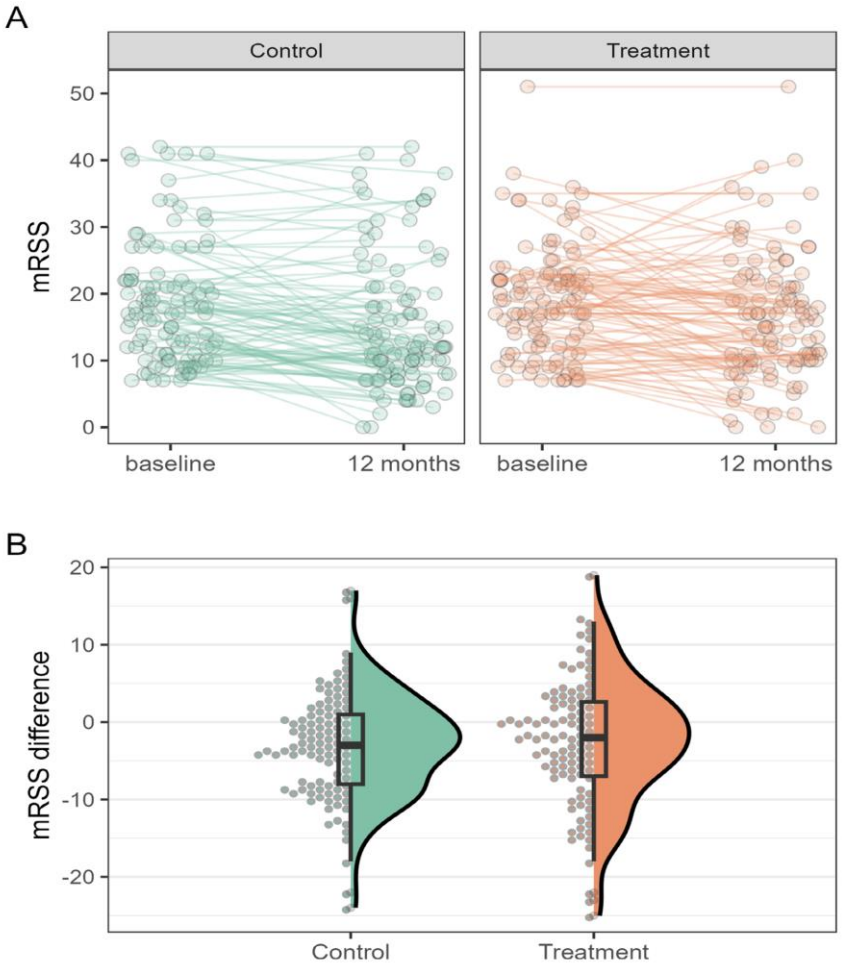
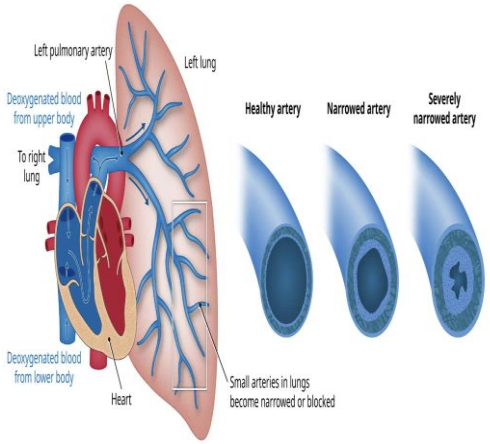


Table 2. Primary and secondary outcomes for the main study*

		Controls		Treatment		
	Overall value	Value	% missing data	Value	% missing data	*P*
Primary outcome						
mRSS difference[a]	−2.9 (7.4)	−3.2 (6.8)	0	−2.6 (8.0)	0	0.55
Secondary outcomes						
Progressive skin fibrosis, n (%)	25 (12)	10 (10)	0	15 (14)	0	0.39
Progressive lung fibrosis, n (%)	41 (27)	23 (29)	23	18 (26)	34	0.83
Regressive skin and lung fibrosis, n (%)	83 (49)	41 (47)	15	42 (51)	21	0.48
Renal crisis, n (%)	2 (1)	1 (1)	0	1 (1)	0	0.99

* *P* values are provided by paired *t*-test for continuous variables and McNemar test for categorical variables. mRSS, modified Rodnan skin score.
[a] Between-group mean difference of mRSS at 12 ± 3 months from baseline.

Mongin D et al. Arthritis Care Res (Hoboken) 2025;77:649-657



Recommendation

for Pulmonary Arterial Hypertension (PAH)

Organ Involvement	Recommendation	LoE	SoR	LoA (SD)	% LoA >8
SSc-PAH	Combination of PDE5i and endothelin receptor antagonists should be considered as first line treatment of SSc PAH.	1A	(A)	8.1 (2.9)	80
	Intravenous Epoprostenol should be considered for the treatment of SSc patients with advanced PAH (Class III and IV)	1A	(A)	7.7 (3.1)	76
	Other Prostacyclin analogues or agonists should be considered for the treatment of SSc PAH	1B	(B)	7.7 (3.1)	76
	Riociguat can be considered for treatment of SSc PAH.	1B	(B)	8.0 (2.4)	76
	The use of anticoagulants (warfarin) for the treatment of SSc-PAH is not recommended.	2A	(C)	8.2 (2.1)	68

- **NEW** – Selexipag
  - GRIPHON study – Of PAH-CTD subgroup (334pts), PAH was associated with SSc in 170
  - Selexipag reduced the risk of composite morbidity/mortality events in patients with PAH-CTD by 41% (HR 0.59; 95% CI 0.41-0.85).
- **NEW** – anticoagulants (warfarin) NOT recommended
  - Metanalysis of 4 CTD-PAH studies, 392pts with SSc-PAH
  - significant increase in mortality associated with the use of anticoagulants (HR 1.58 (95% CI 1.08 to 2.31); p=0.02)

EULAR recommendations for the treatment of systemic sclerosis: 2023 update

Francesco Del Galdo [1,2] Alain Lescoat [3] Philip G Conaghan [1,2] Eugenia Bertoldo,[4] Jelena Čolić,[5] Tânia Santiago [6] Yossra A Suliman,[7,8] Marco Matucci-Cerinic [9] Armando Gabrielli,[10] Oliver Distler [11] Anna-Maria Hoffmann-Vold [12] Ivan Castellví [13] Alexandra Balbir-Gurman,[14] Madelon Vonk [15] Lidia Ananyeva,[16] Simona Rednic,[17] Anna Tarasova,[18] Pedrag Ostojic,[19] Vladimira Boyadzhieva,[20] Khadija El Aoufy,[21] Sue Farrington,[22,23] Ilaria Galetti,[23] Christopher P Denton [24] Otylia Kowal-Bielecka,[25] Ulf Mueller-Ladner,[26] Yannick Allanore [27]

Del Galdo F, *et al. Ann Rheum Dis* 2024;**0**:1–12. doi:10.1136/ard-2024-226430

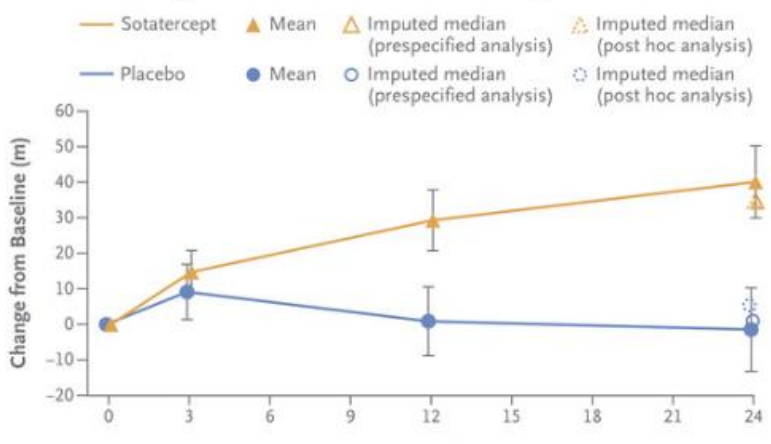
RESEARCH SUMMARY

Phase 3 Trial of Sotatercept for Treatment of Pulmonary Arterial Hypertension

Hoeper MM et al. DOI: 10.1056/NEJMoa2213558

A total of 163 patients were assigned to receive sotatercept and 160 to receive placebo (19-29 CTD-PAH)

Change in 6-Minute Walk Distance through Week 24



Adverse Events of Interest or Special Interest

	Sotatercept (N=163)	Placebo (N=160)
	no. of patients (%)	
Increased hemoglobin	9 (5.5)	0
Thrombocytopenia	10 (6.1)	4 (2.5)
Bleeding events	35 (21.5)	20 (12.5)
Increased blood pressure	6 (3.7)	1 (0.6)
Telangiectasia	17 (10.4)	5 (3.1)

CONCLUSIONS

In adults with pulmonary arterial hypertension receiving stable background therapy, the addition of subcutaneous sotatercept every 21 days resulted in a greater improvement in exercise capacity over a period of 24 weeks than placebo.

N Engl J Med 2023 Apr 20;388(16):1478-1490

The NEW ENGLAND JOURNAL of MEDICINE

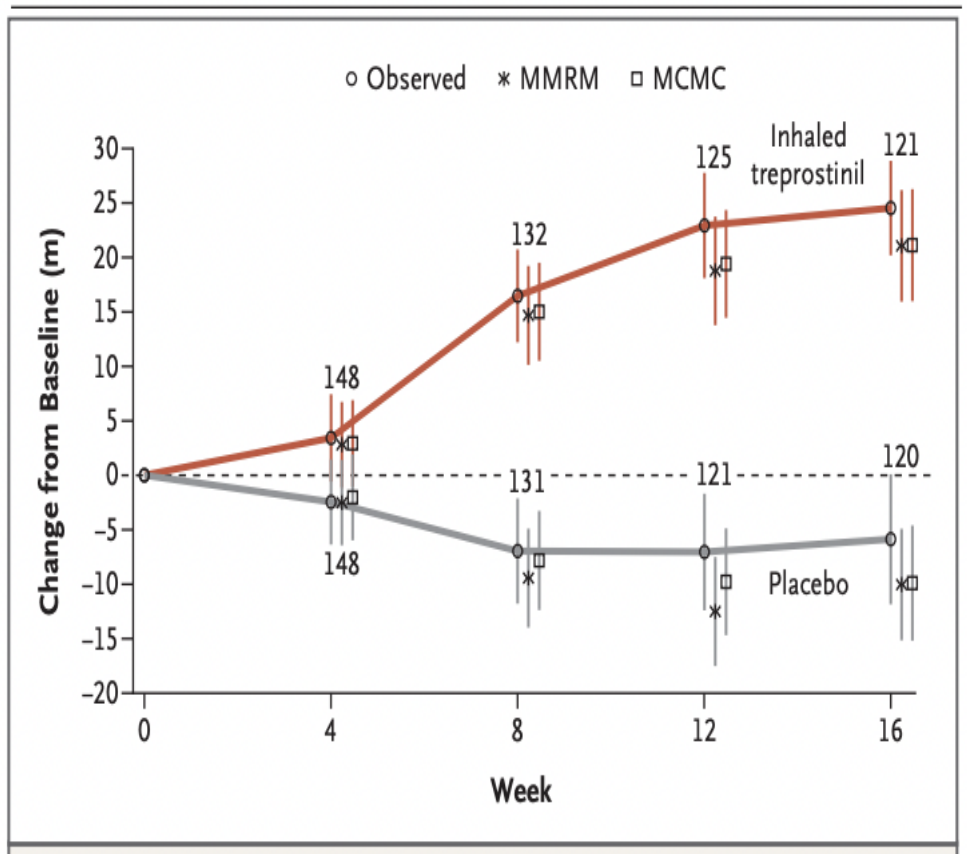
Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

Aaron Waxman, M.D., Ph.D., Ricardo Restrepo-Jaramillo, M.D., Thenappan Thenappan, M.D., Ashwin Ravichandran, M.D., Peter Engel, M.D., Abubakr Bajwa, M.D., Roblee Allen, M.D., Jeremy Feldman, M.D., Rahul Argula, M.D., Peter Smith, Pharm.D., Kristan Rollins, Pharm.D., Chunqin Deng, M.D., Ph.D., Leigh Peterson, Ph.D., Heidi Bell, M.D., Victor Tapson, M.D., and Steven D. Nathan, M.D.

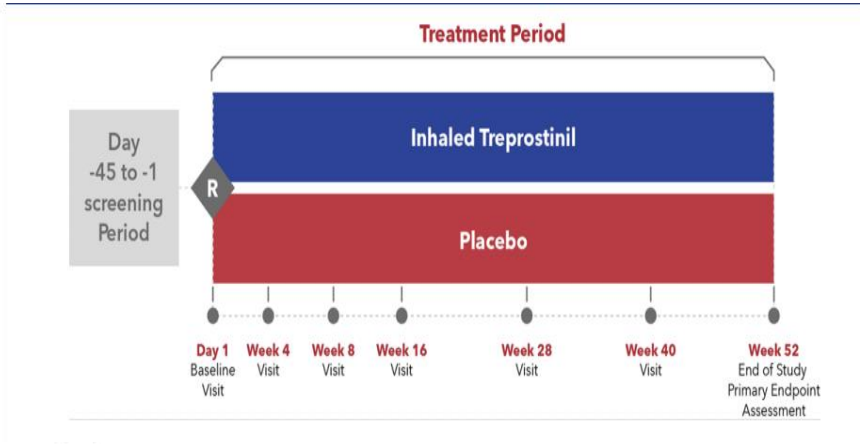
2021 Jan 28;384(4):325-334

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Inhaled Treprostinil (N=163)	Placebo (N=163)	All Patients (N=326)
Female sex — no. (%)	85 (52.1)	68 (41.7)	153 (46.9)
Mean age at randomization (range) — yr	65.6 (26–90)	67.4 (36–85)	66.5 (26–90)
Age distribution — no. (%)			
<65 yr	64 (39.3)	48 (29.4)	112 (34.4)
65 to <80 yr	83 (50.9)	100 (61.3)	183 (56.1)
≥80 yr	16 (9.8)	15 (9.2)	31 (9.5)
Race or ethnic group — no. (%)†			
White	112 (68.7)	126 (77.3)	238 (73.0)
Black or African American	41 (25.2)	30 (18.4)	71 (21.8)
American Indian or Alaska Native	2 (1.2)	1 (0.6)	3 (0.9)
Asian	7 (4.3)	5 (3.1)	12 (3.7)
Multiple	0	1 (0.6)	1 (0.3)
Unknown	1 (0.6)	0	1 (0.3)
Hispanic or Latino ethnic group — no. (%)†			
Yes	11 (6.7)	16 (9.8)	27 (8.3)
No	152 (93.3)	146 (89.6)	298 (91.4)
Data missing	0	1 (0.6)	1 (0.3)
Mean time since diagnosis — yr	0.54±1.16	0.54±1.31	0.54±1.23
Cause of lung disease — no. (%)			
Idiopathic interstitial pneumonia	65 (39.9)	81 (49.7)	146 (44.8)
Chronic hypersensitivity pneumonitis	10 (6.1)	9 (5.5)	19 (5.8)
Occupational lung disease	5 (3.1)	1 (0.6)	6 (1.8)
Combined pulmonary fibrosis and emphysema	42 (25.8)	40 (24.5)	82 (25.2)
Connective tissue disease	40 (24.5)	32 (19.6)	72 (22.1)
Other	1 (0.6)	0	1 (0.3)



TETON-2 study: Multinational Study of Efficacy and Safety of Inhaled Treprostinil in Subjects With Idiopathic Pulmonary Fibrosis



SELECTED KEY INCLUSION CRITERIA

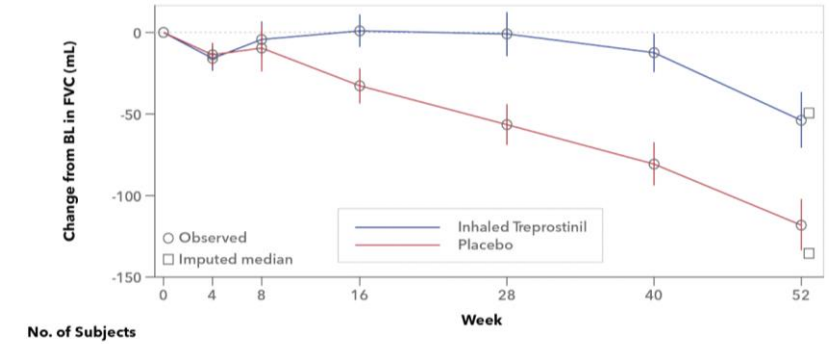
- Age 40+
- FVC[2] ≥ 45% predicted
- If on pirfenidone or nintedanib:
  - stable dose for ≥ 30 days prior to baseline
- Diagnosis of IPF[3,4]
- HRCT[5] within the last 12 months[6]

SELECTED KEY EXCLUSION CRITERIA

- Primary obstructive disease, FEV_1[7]/FVC < 0.70
- >10 L/min of supplemental oxygen use at baseline
- Use of PAH[8] agents 60 days prior to baseline[9]
- IPF exacerbations or infections[10]

Primary Endpoint

Change from Baseline in Absolute FVC at 52 Weeks

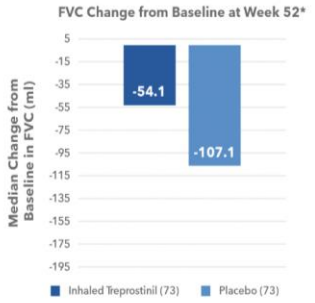


95.6 mL*
(95% CI, 52.2, 139.0)
P<0.0001

*(H-L estimate)

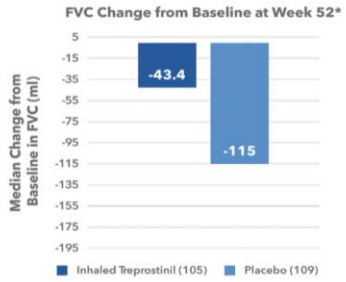
Hodges-Lehmann estimate and non-parametric aligned stratified rank Wilcoxon test

No Background Therapy



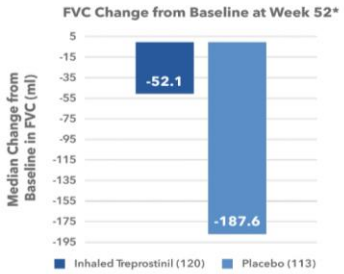
43.9 mL (H-L estimate)
(95% CI, -45.0, 132.8);
P=0.3329

Background Nintedanib

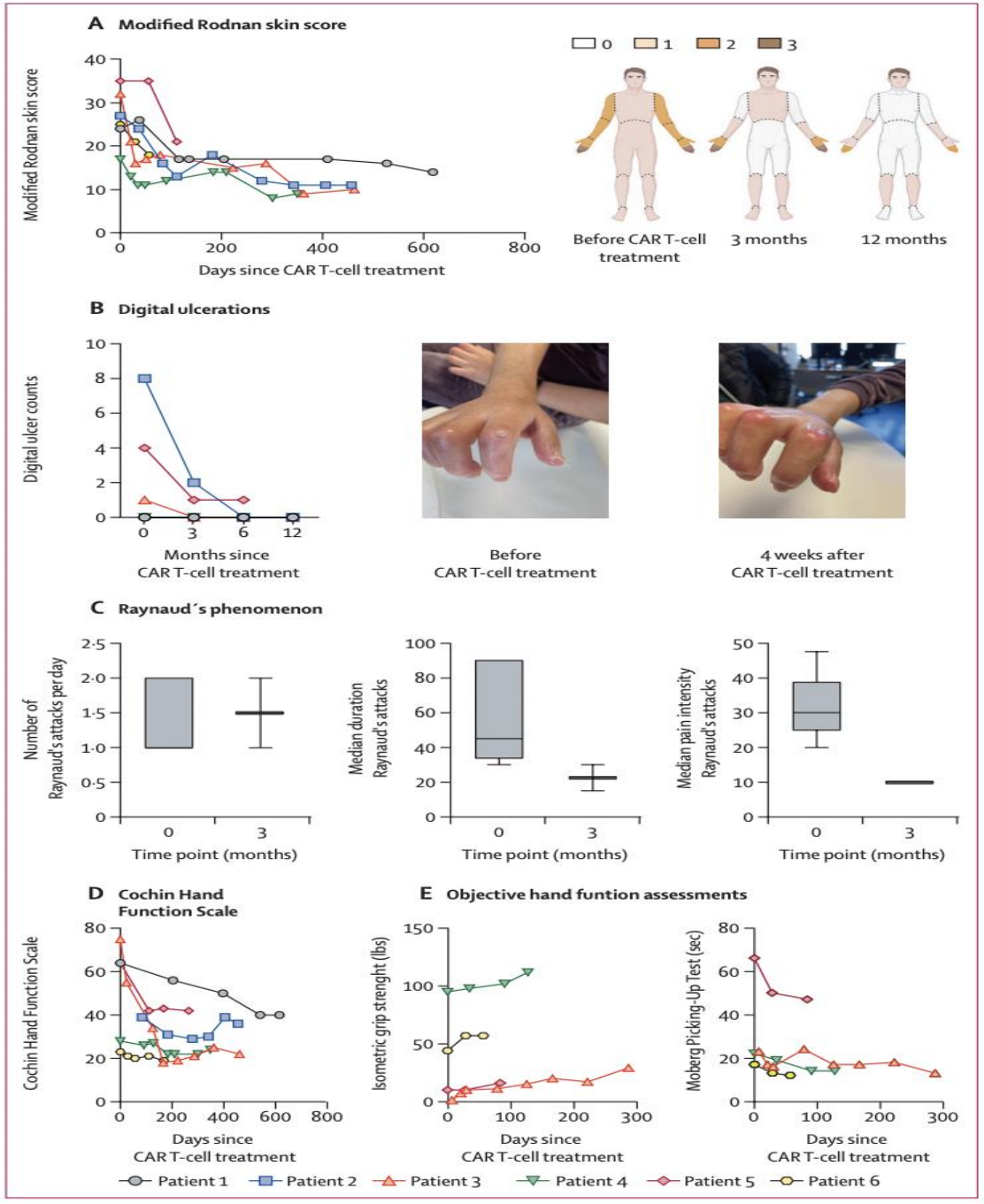


97.6 mL (H-L estimate)
(95% CI, 26.1, 169.2);
P=0.0075

Background Pirfenidone



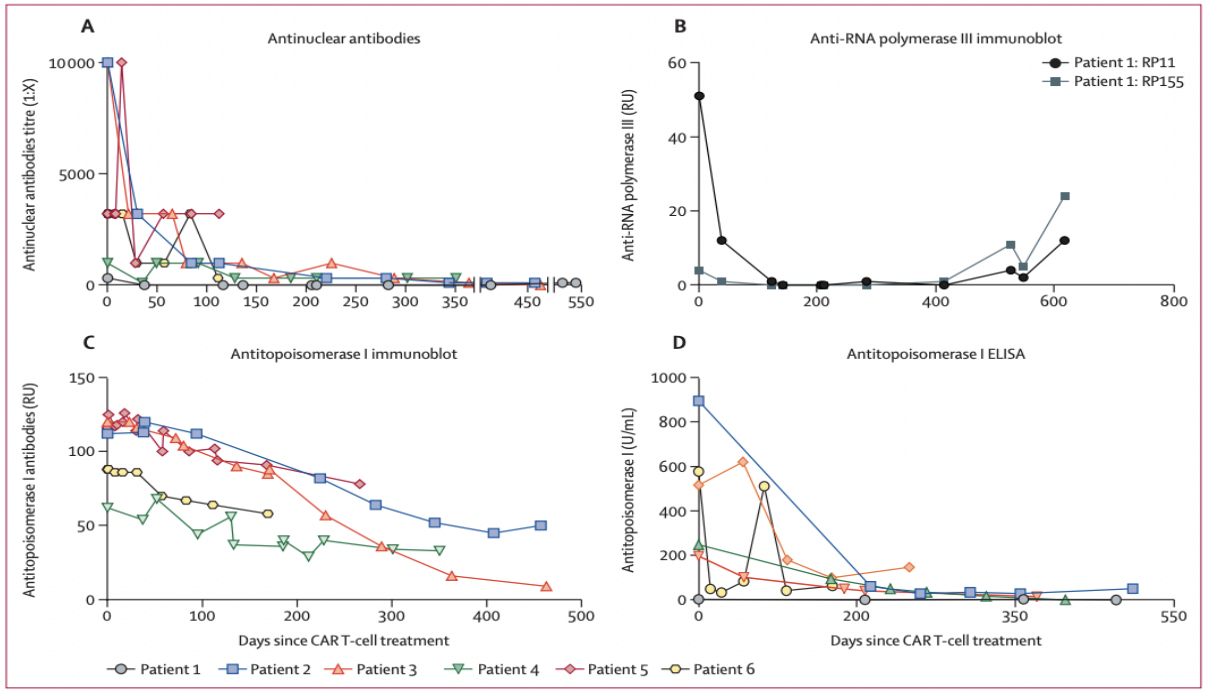
127.9 mL (H-L estimate)
(95% CI, 58.8, 196.9);
P=0.0003



6 patients
Baseline mRSS: 26
Disease duration: 36m
Age: 42

31% improvement at 1 year

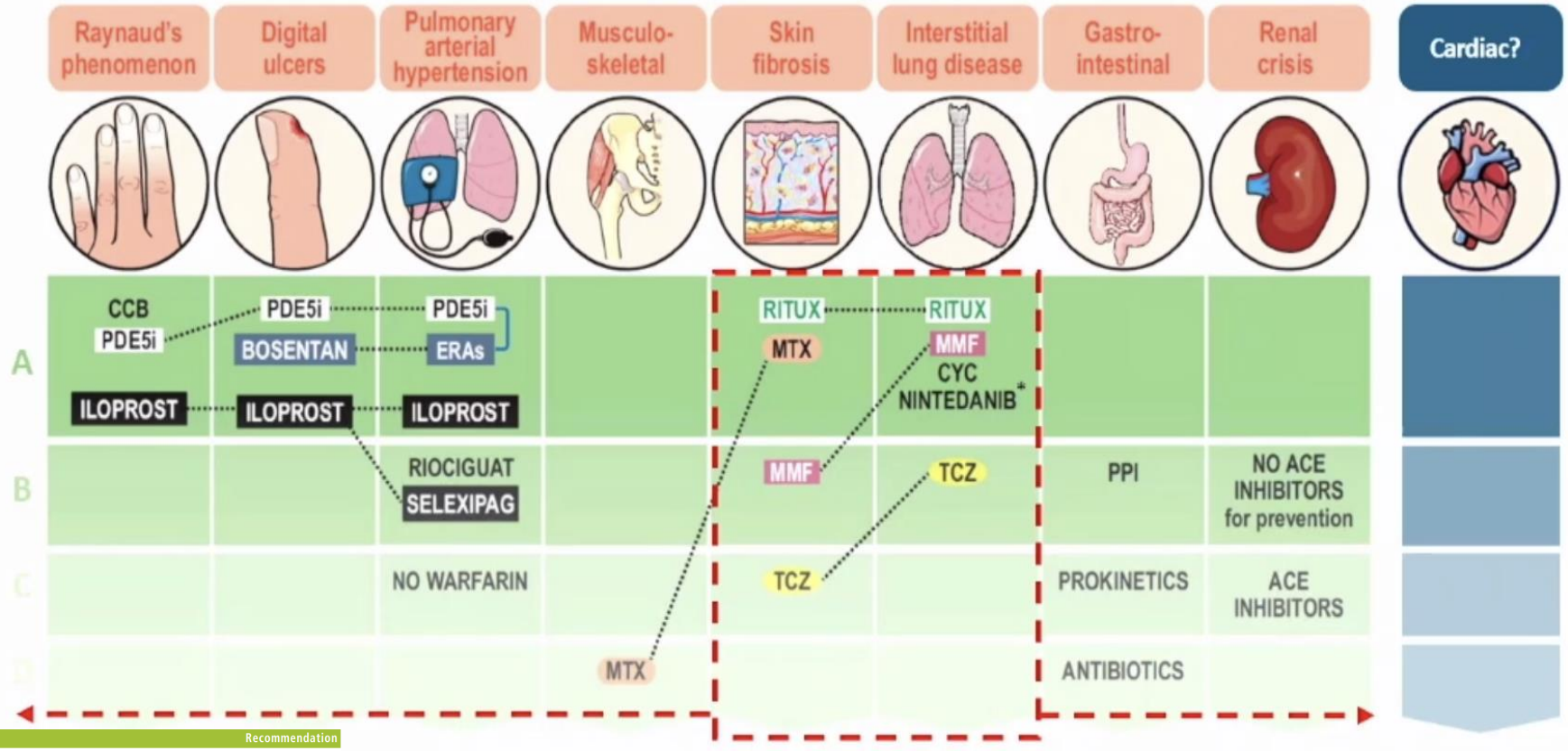
THE LANCET
Rheumatology



CD19-targeting CAR T-cell therapy in patients with diffuse systemic sclerosis: a case series

Janina Auth, Fabian Müller*, Simon Völkl, Nadine Bayerl, Jörg H W Distler, Carlo Tur, Maria G Raimondo, Sara Chenguiti Fakhouri, Armin Atzinger, Birte Coppers, Markus Eckstein, Anna-Maria Liphardt , Tobias Bäuerle, Koray Tascilar , Michael Aigner, Sascha Kretschmann, Andreas Wirsching , Jule Taubmann, Melanie Hagen, Andrea-Hermina Györfi, Soraya Kharboutli, Tobias Krickau, Clara Dees, Silvia Spörl, Tobias Rothe, Thomas Harrer, Aline Bozec, Ricardo Grieshaber-Bouyer, Florian Fuchs, Torsten Kuwert, Carola Berking, Raymund E Horch, Michael Uder, Andreas Mackensen, Georg Schett, Christina Bergmann*

SSc: what are we treating?



Recommendation

EULAR recommendations for the treatment of systemic sclerosis: 2023 update

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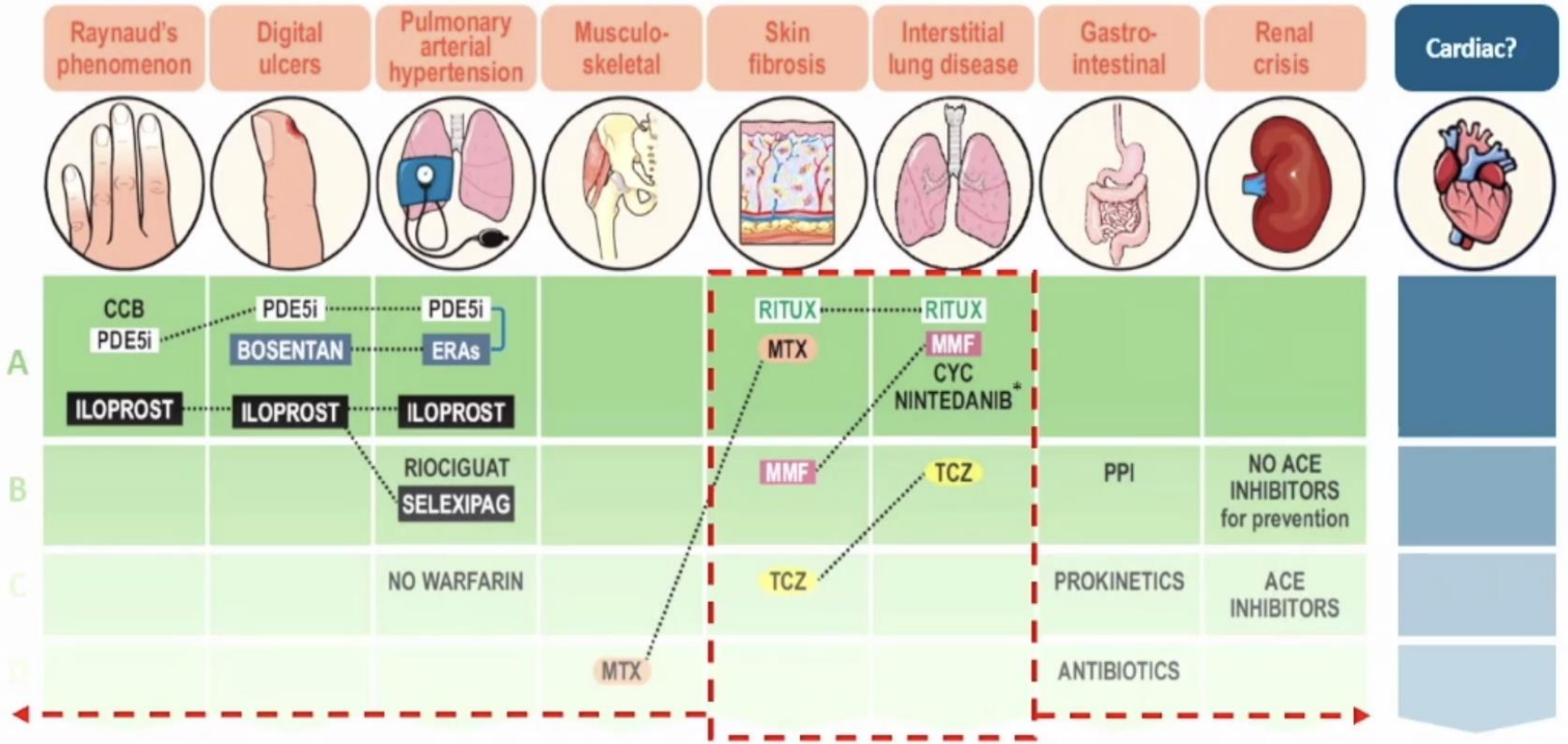
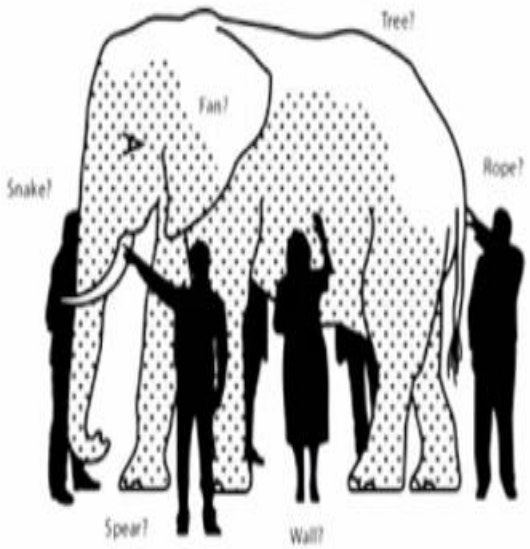
SSc: what are we treating?





In conclusion

- A one-size-fits-all strategy cannot be implemented in SSc
- Clinical and immunological phenotype

- Emerging role of inflammation in early-diffuse disease (tocilizumab)

- Immunosuppression for SSc-ILD and skin fibrosis
  - MMF
  - RTX
  - TCZ
- Nintedanib for SSc-ILD, alone or with MMF/bDMARDs

- Up-front combination therapy (PDE5i + ERA) for SSc – PAH

- More trials needed for GI and cardiac involvement