

Szisztémás sclerosis és rokon kórképek



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DE ÁOK Reumatológiai Tanszék

KK Reumatológiai és Immunológiai Klinika



Klinikai immunológia és allergológia II. Klinikum

Semmelweis Egyetem

Reumatológiai és Immunológiai Klinika

2026. Szeptember 29.

Szisztémás sclerosis

Patogenezis



Tünetek



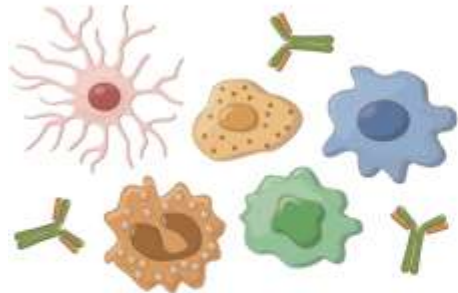
Diagnosztika



Terápia

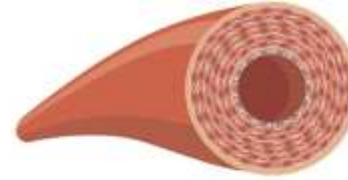
- Microbial infection
- Toxic exposure : Silica, solvents..
- Oxidative stress
- Immune response

Triggers



Immune cell activation

- Innate immunity
- Adaptive immunity
- Autoimmunity



- Endothelial cell injury
- Endothelial cell dysfunction
- Defective vascular remodeling
- EndoMT, EMT, AMT

Vasculopathy

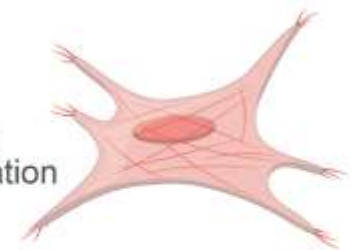
SSc Pathogenesis

Genetic susceptibility

Environmental factors

Fibrosis

- Excessive ECM deposition
- Persistent fibroblasts activation



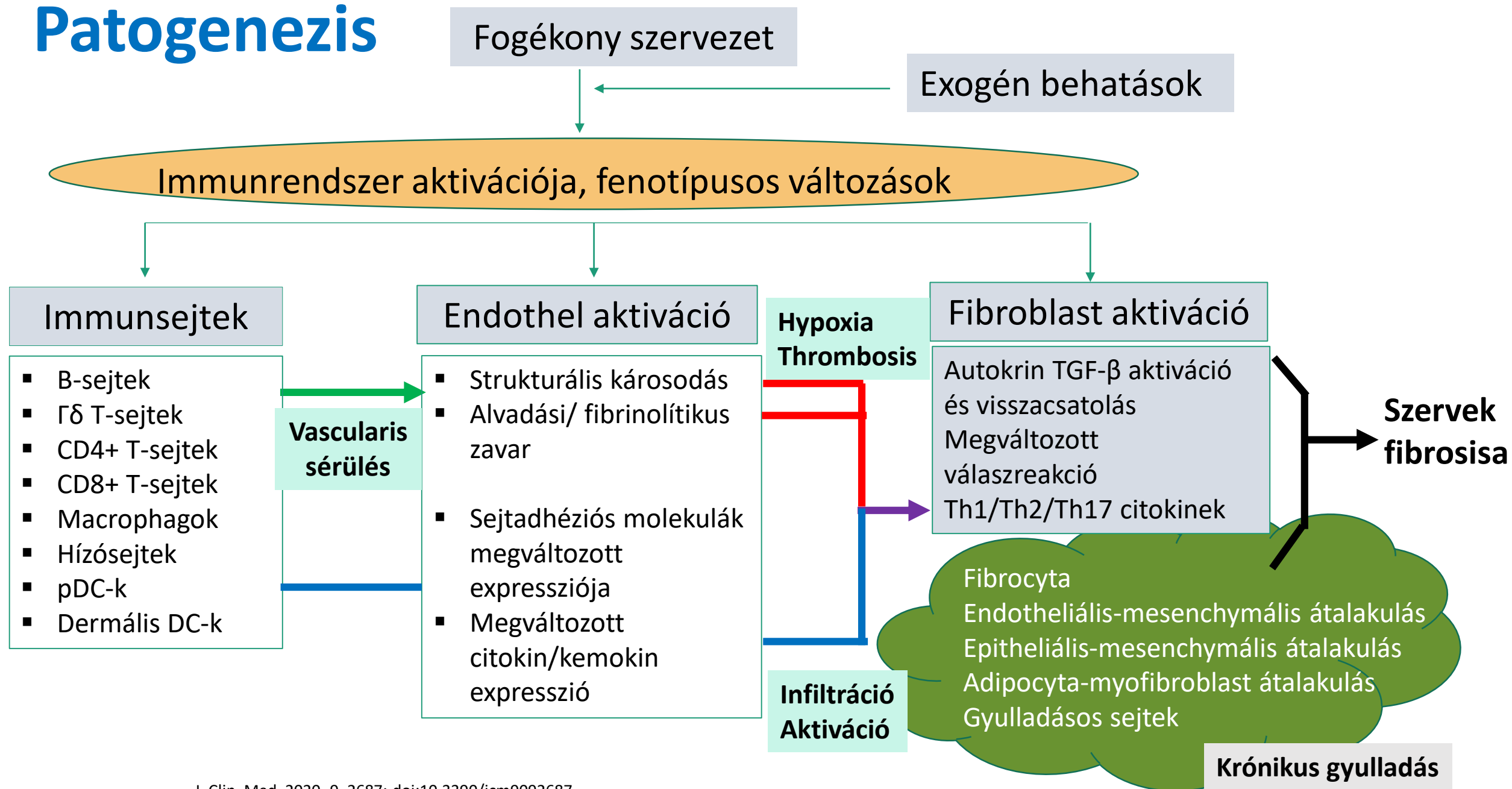
Chronic inflammation / Organ damage



Table 1. The summary data of the annotated loci associated with SSc trait including all associations with p values below 8×10^{-8} according to the GWAS catalog (<http://www.ebi.au.uk/gwas/>)

Chromosome	Mapped gene	Reported trait	Ancestry	Chromosome	Mapped gene	Reported trait	Ancestry
1p34.3	KIAA0319L	SSc, SLE	EUR	7p15.2	JAZF1	SSc, SLE	EUR
1p31.3	IL12RB2	SSc, RA, IIM, SLE, CD	EUR	7q11.23	EIF4H, LIMK1	SSc, RA, IIM, SLE	EUR
1p13.2	PTPN22, AP4B1-AS1	SSc, RA, IIM, SLE	EUR	7q32.1	TNPO3	SSc, RA, IIM, SLE	EUR, AA, AC
1q21.3	FLG-AS1, FLG2	SSc	EAS		IRF5, KCP	SSc, RA, IIM, SLE	EUR, AA, AC
1q23.3	FCGR2B, FCGR3B	SSc	EUR, AA, AC		TPI1P2, CYCSP20	SSc, SLE	EUR, AA, AC, EAS
	Y_RNA, RPL31P11	SSc	EAS		RNU6-177P, LINC03072	SSc	EAS
1q24.2	CD247	SSc	EUR	8p23.1	FAM167A, BLK	SSc, RA, IIM, SLE	EUR, AA, AC, EAS
1q25.1	TNFSF4, PRDX6-AS1	SSc, RA, IIM, SLE	EUR, EAS	8q12.1	LINC01301	SSc	EUR, EAS
1q25.3	SMG7, NCF2	SSc, RA, IIM, SLE	EUR	8q12.2	CHD7, RAB2A	SSc	EUR
2q32.2	NAB1, GLS	SSc, RA, IIM, SLE	EUR	11p15.5	SCT, DRD4	SSc, RA, IIM, SLE	EUR
2q32.3	STAT4	SSc, RA, IIM, SLE	EUR, AA, EAS		RNU6-878P, CD81-AS1, CDHR5	SSc	EUR
3p24.1	LINC01967	SSc	EUR, EAS	11q23.3	CXCR5, Y_RNA	SSc	EUR
3p14.3	DNASE1L3	SSc, RA, IIM, SLE	EUR		DDX6	SSc	EUR, EAS
	PXK	SSc, SLE	EUR, EAS	12q13.2	ESYT1, ZC3H10	SSc	EUR
	FLNB	SSc	EUR, EAS	12q15	IFNG-AS1	SSc (ACA-positive)	EAS
3q13.33	ARHGAP31	SSc	EUR, EAS	12q24.13	PTPN11	SSc	EUR
3q25.33	IL12A-AS1	SSc	EUR, EAS	13q13.3	NBEA	SSc-ILD	EAS
	ARL14, RPL6P8	SSc, RA, IIM, SLE	EUR	14q32.33	AHNAK2, IGHM	SSc	EUR, EAS
4p16.3	DGKQ	SSc, RA, IIM, SLE	EUR, EAS	15q24.1	CSK	SSc	EUR, EAS
4q24	NFKB1	SSc	EUR, EAS	15q24.2	Metazoa_SRP, RPL36AP45	SSc, SLE	EUR
4q28.3	STMN1P2, RPS23P2	SSc (ACA-positive)	EAS	16p11.2	ITGAM	SSc, SLE	EUR
4q34.3	RNA5SP173, NDUFB5P1	SSc	EUR, EAS	16q24.1	IRF8-LINC01082, LINC02132	SSc, RA, IIM, SLE	EUR, AA, AC, EAS
4q35.1	UFSP2, ANKRD37	SSc	EAS	17q21.1	GSDMA, GSDMB	SSc	EUR, EAS
5q31.1	IRF1	SSc, CD	EUR		STAT3	SSc, CD	EUR
5q33.1	TNIP1	SSc, RA, IIM, SLE	EUR, EAS	17q25.1	NUP85	SSc	EUR, EAS
5q33.3	MIR3142HG	SSc, RA, IIM, SLE	EUR	19p13.2	TYK2	SSc, RA, IIM, SLE	EUR
6p21.32	HLA-region	SSc	EUR, EAS	19p13.11	IL12RB1	SSc	EUR, EAS
	MTCO3P1, NOTCH4, TSBP1-AS1	SSc	EUR	19q13.33	PRR12	SSc, RA, IIM, SLE	EUR
6p21.31	ZBTB9, GGNBP1	SSc, CD	EUR	20q13.12	SLC12A5	SSc	EUR, EAS
6q21	ATG5	SSc, RA, IIM, SLE	EUR, EAS	20q13.33	RTEL1-TNFRSF6B, RTEL1	SSc (ACA-positive)	EAS
6q23.3	TNFAIP3, SIMALR	SSc, RA, IIM, SLE	EUR, EAS	22q11.21	YDJC, CCDC116	SSc, RA, IIM, SLE	EUR
	LINC02539, WAKMAR2	SSc, SLE	EUR				

Patogenezis



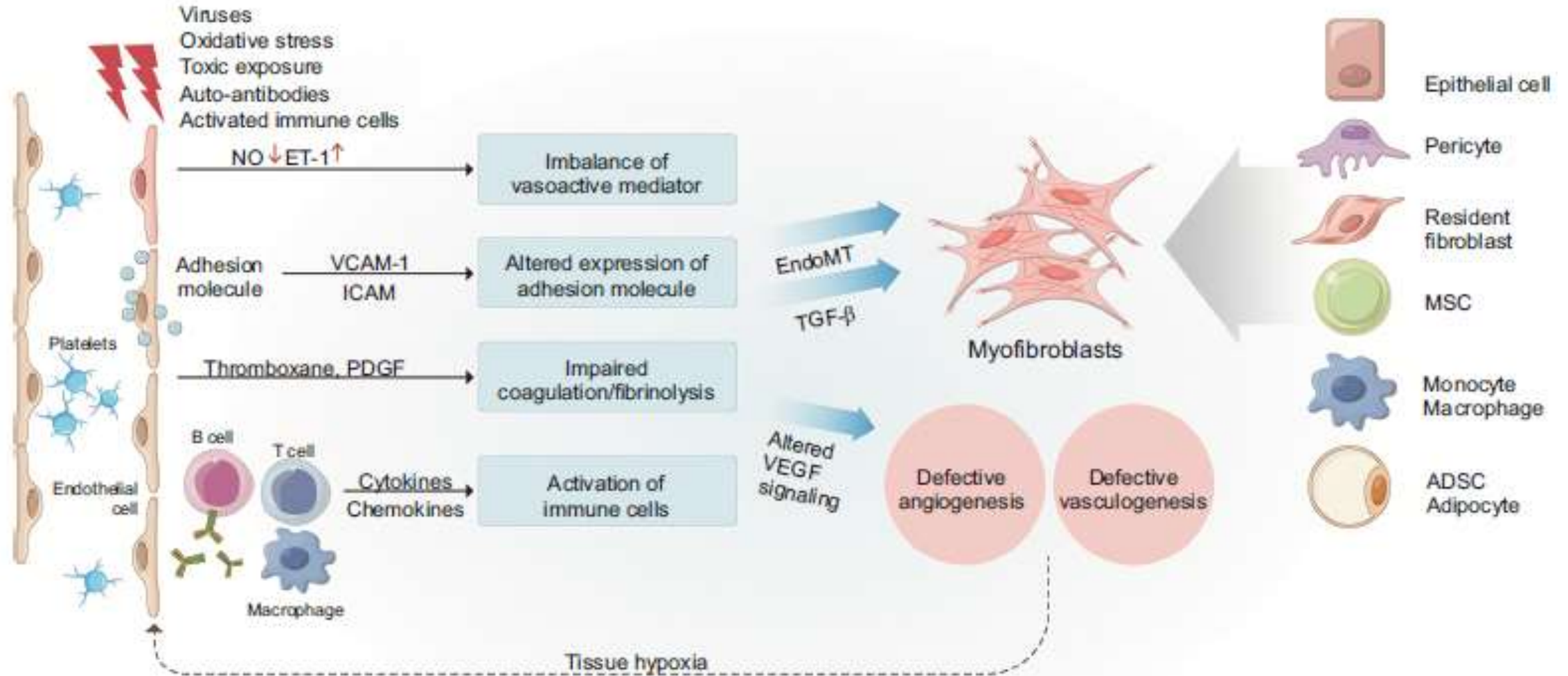


Figure 2. A pathologic association between vasculopathy and fibrosis in SSc. ECs are subjected to damage and dysfunction due to

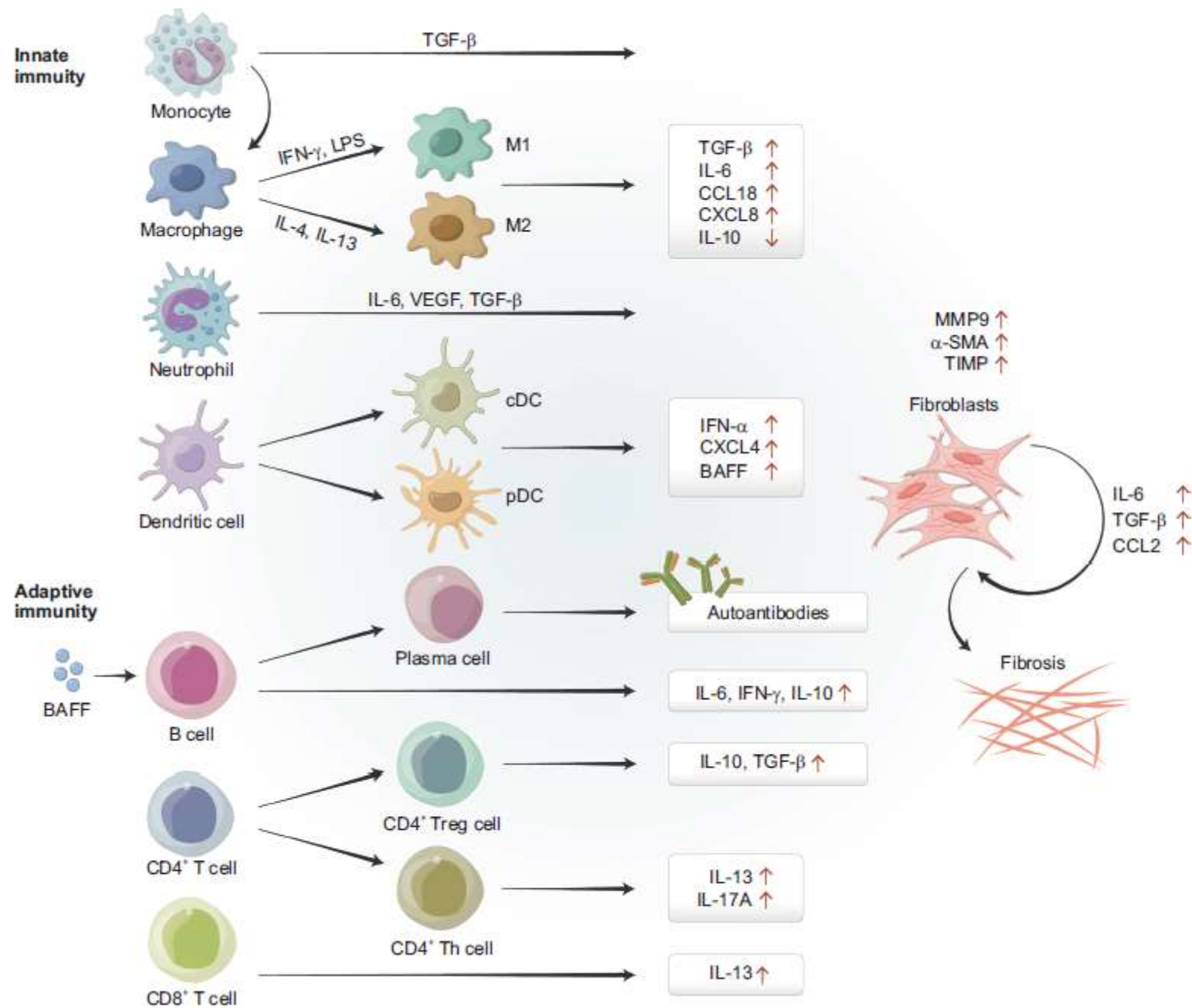


Figure 3. The pro-inflammatory and profibrotic network involved in the pathogenesis of SSc. This figure highlights the intricate

Raynaud tünet

Vazokonstriktio ↑

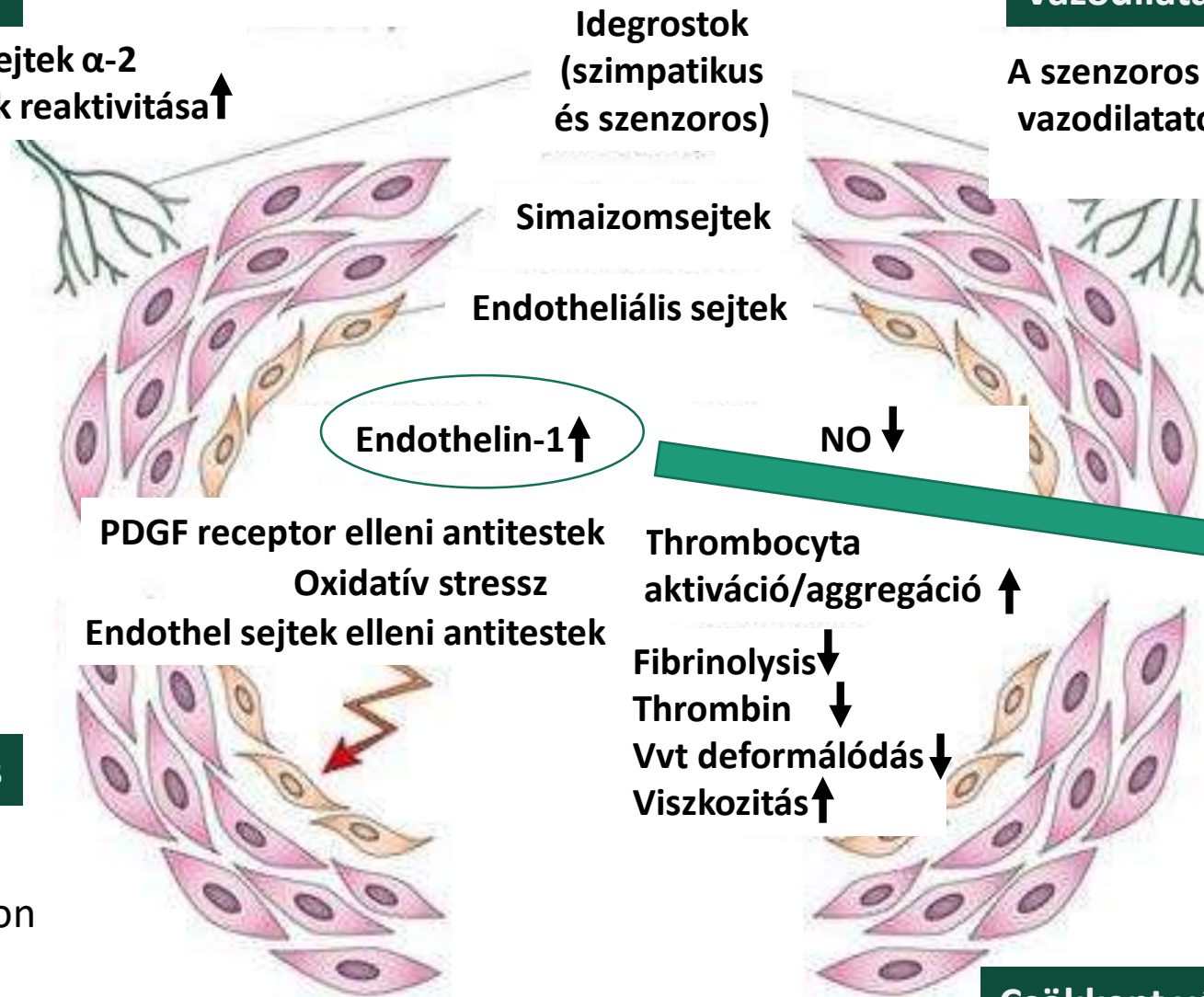
A simaizomsejtek α -2
adrenoreceptorok reaktivitása ↑



A digitalis artériák hideghatásra,
vagy emocionális stresszre
bekövetkező kóros válaszreakciója,
fokozott vasokonstriktioja

Endothel sérülés

Sejtek közötti adhézió, tight junction
fellazulása



Vazodilatáció ↓

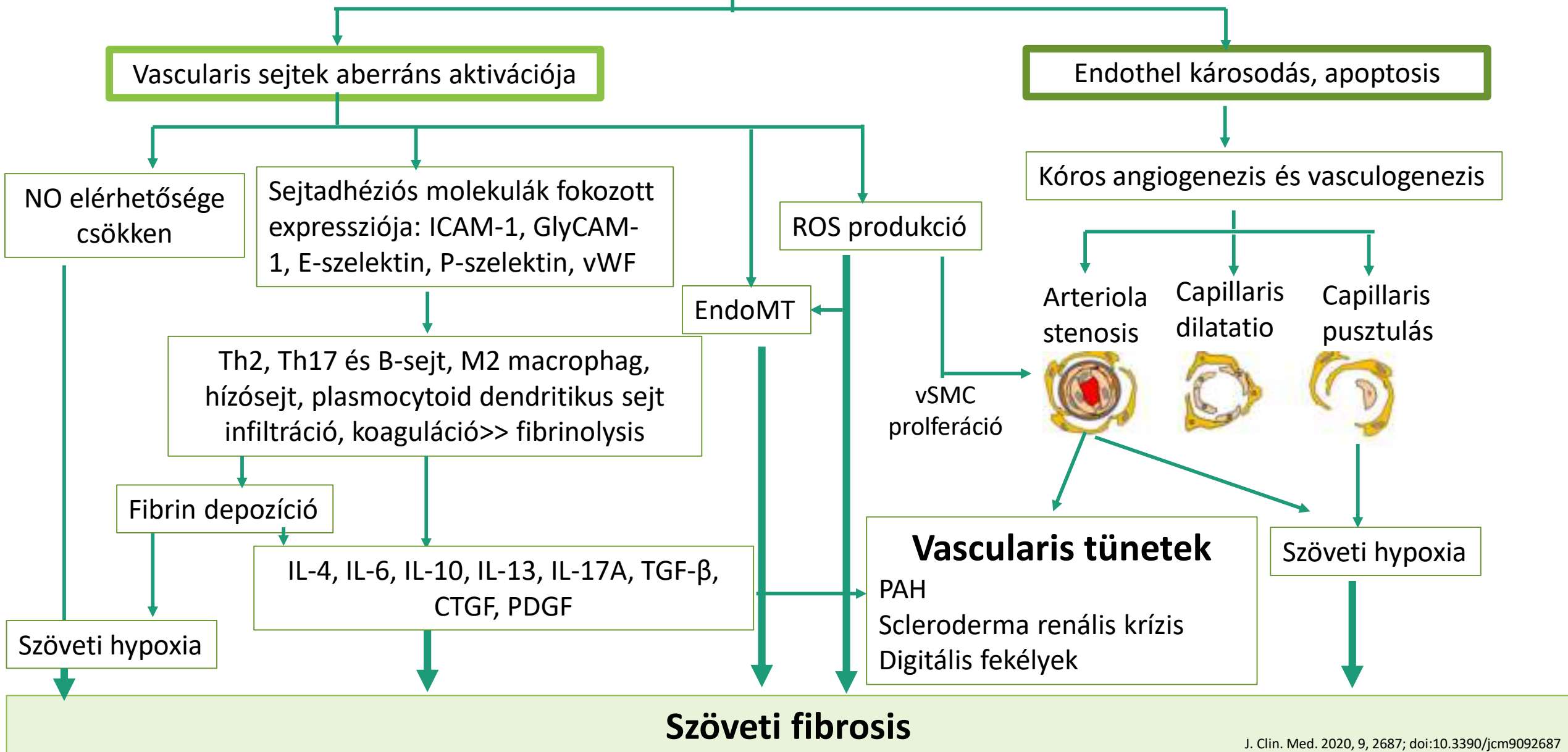
A szenzoros afferens rostokból származó
vazodilatator neuropeptidek (pl. CGRP)
szintje ↓

Csökkent véráramlás/
prokoaguláns állapot

Vasculopathia



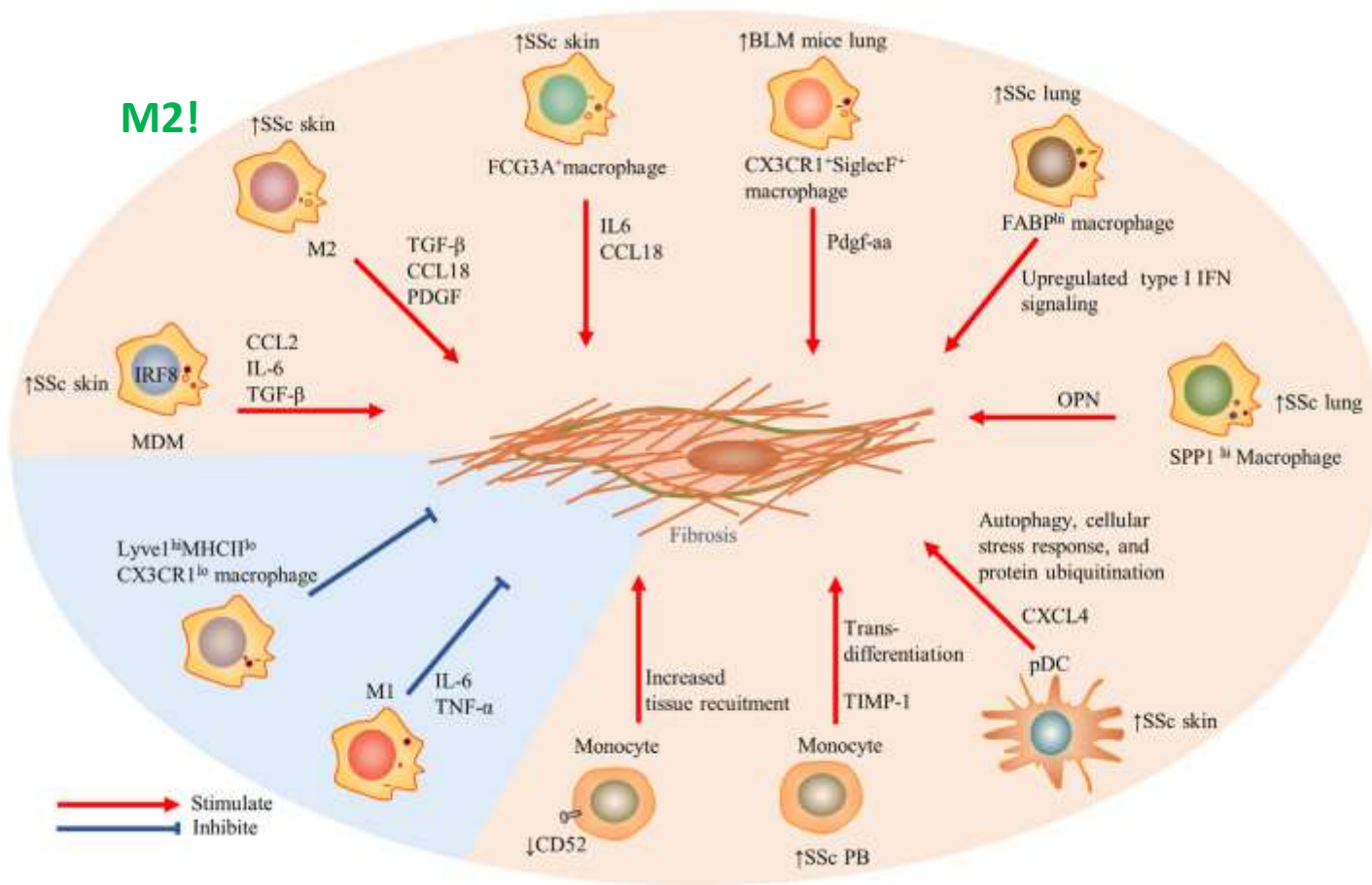
Autoimmunitás (endothel sejt elleni at és egyéb környezeti tényezők)



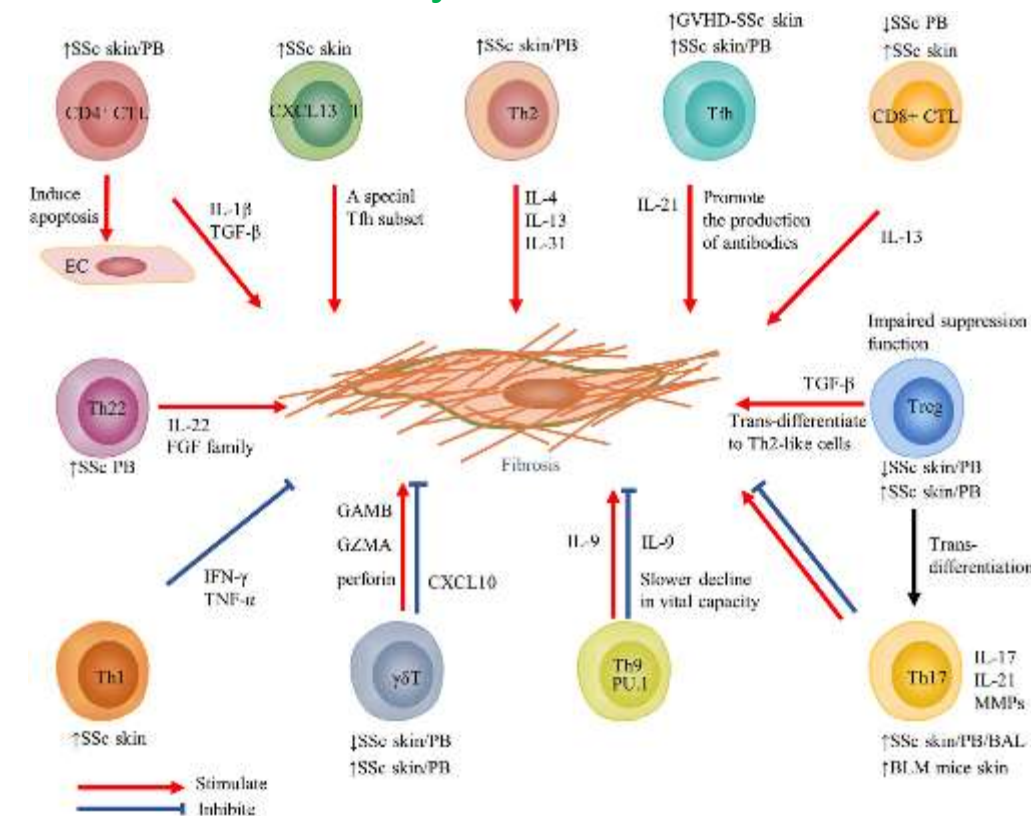
Contributions of Immune Cells and Stromal Cells to the Pathogenesis of

Systemic Sclerosis: Recent Insights

Bingying Dai et al. 2022. Front. Pharmacol. 13:826839.



CXCL13+ T-sejt!

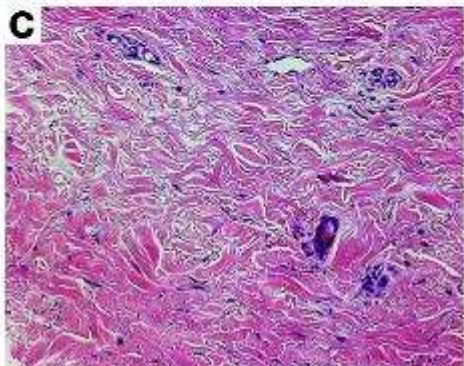
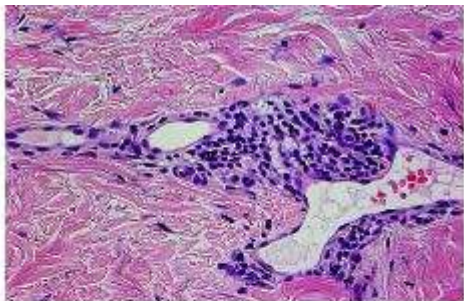


Contribution of T-cell subsets and their cytokines to fibrosis in SSc

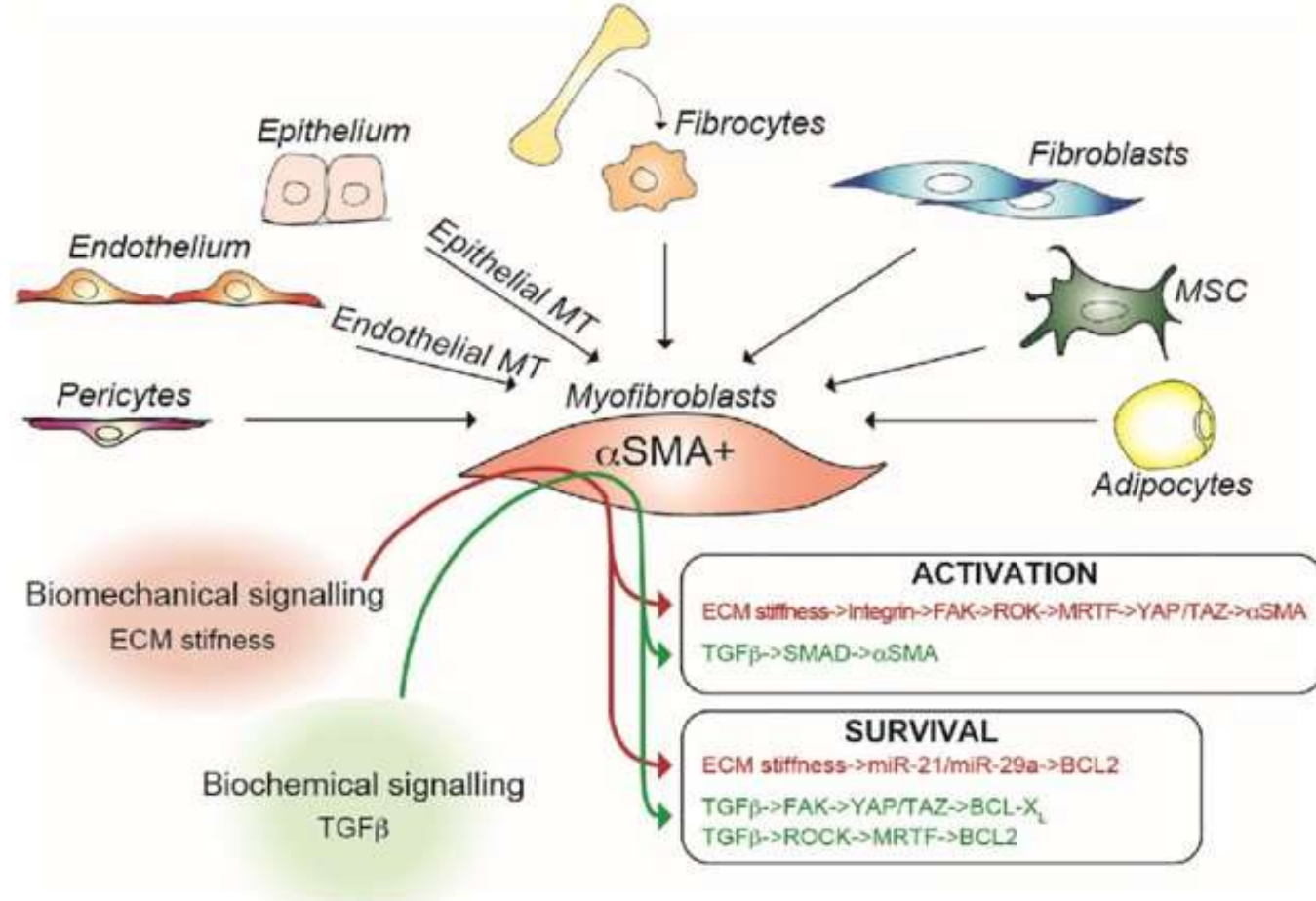
The role of innate immune cells including monocytes, macrophages, and dendritic cells in the fibrosis in SSc.



Fibrosis



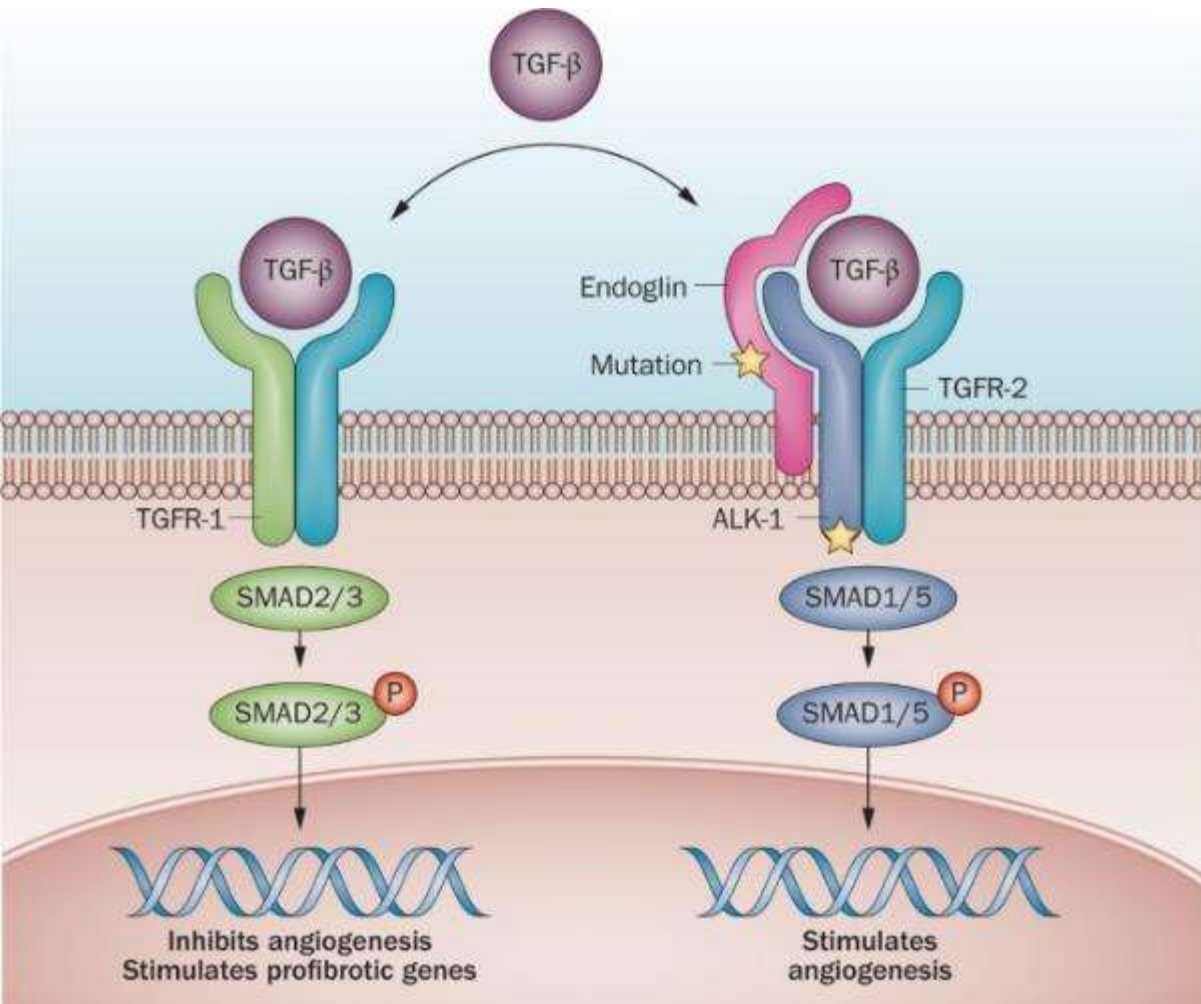
Gyulladásos
mikrokörnyezet
+
Szöveti sérülés, hypoxia,
stressz



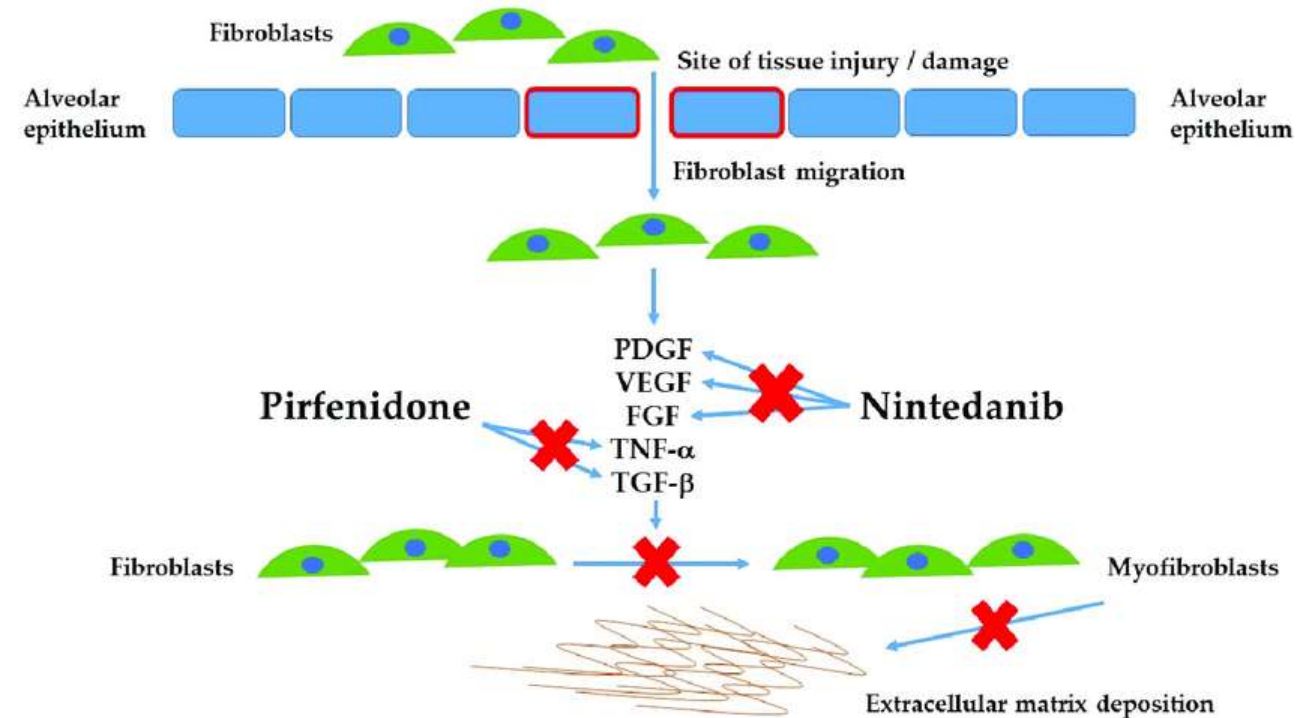
Kóros fibrosis: fibroblast-myofibroblast (α -simaizom aktint expresszáló) átalakulás, fibroblast apoptosis csökkenés, autokrin aktiváció miatt túlzott kollagén és ECM termelés

Megvastagodott kollagén rostok: I, III, VII-es típusú kollagén, subcutan zsírszövet csökken, kollagén keresztkötések

TGF- β



- Fibrosis: központi szerep, ECM termelés fokozása, lebontás gátlása
- Forrása: fibroblasztok, miofibroblasztok, T-sejtek, monociták, makrofágok és vérlemezkék
- I-es típusú kollagén, I-es típusú plazminogén aktivátor inhibitor, CTGF és α -SMA gén expresszió fokozása



Szisztémás sclerosis

Patogenezis



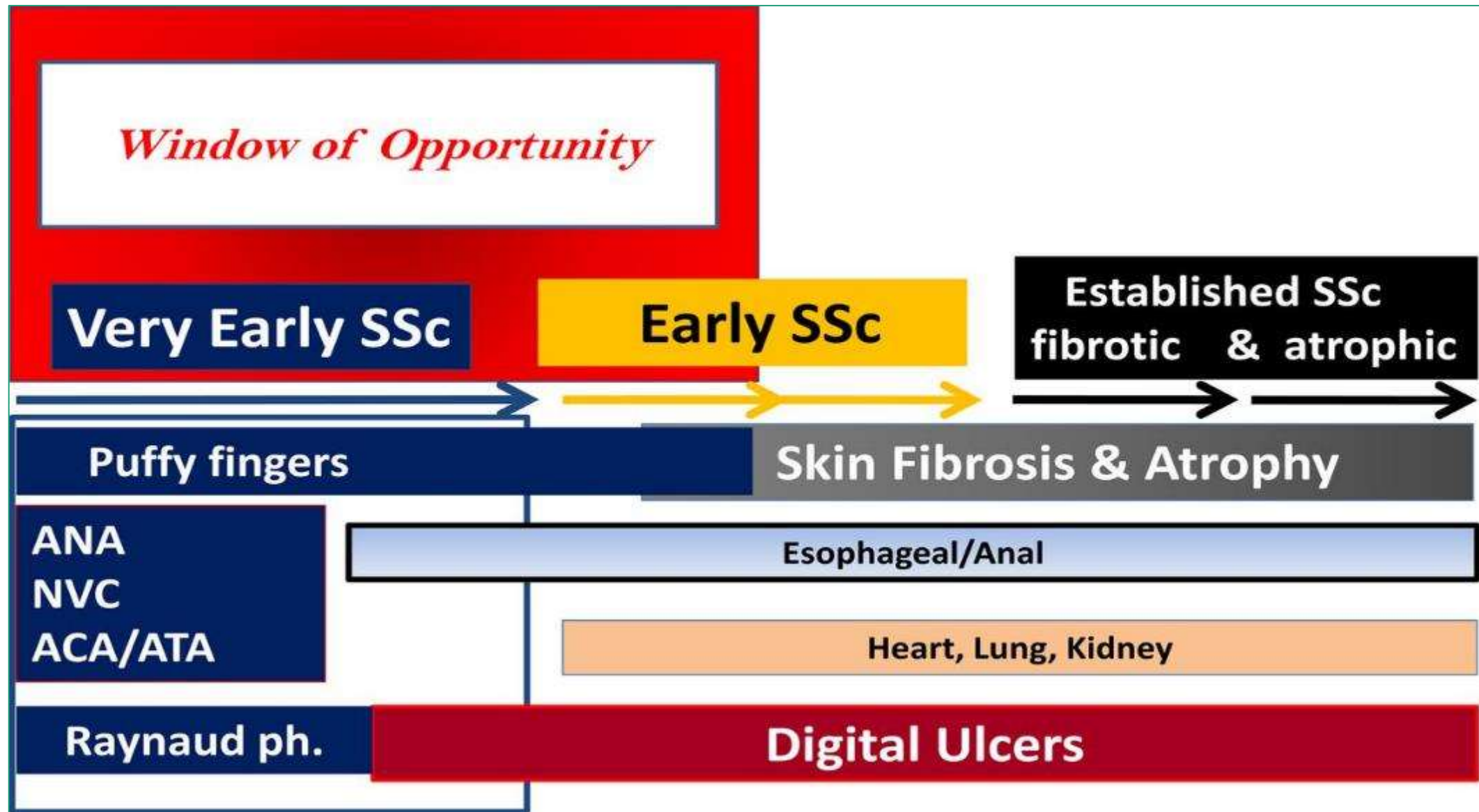
Tünetek



Diagnosztika



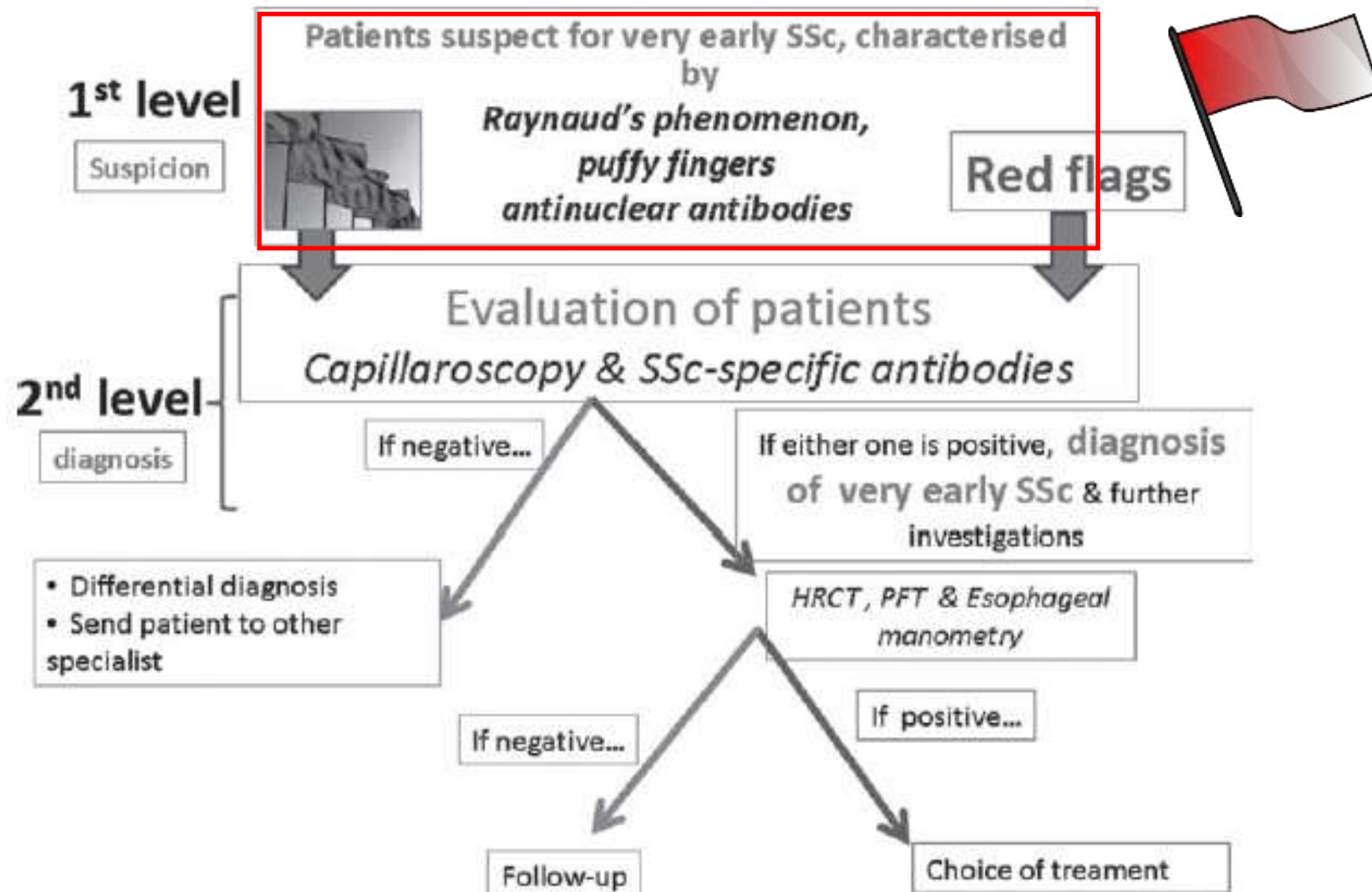
Terápia



Preliminary criteria for the very early diagnosis of systemic sclerosis: results of a Delphi Consensus Study from EULAR Scleroderma Trials and Research Group

Ann Rheum Dis 2011;**70**:476–481. doi:10.1136/ard.2010.136929

J Avouac,¹ J Fransen,² UA Walker,³ V Ricciari,⁴ V Smith,⁵ C Muller,⁶ I Miniati,⁷
IH Tamer,⁸ S Bellando Randone,⁶ M Cutolo,⁹ Y Allanore,¹ O Distler,¹⁰ G Valentini,¹¹
L Czirjak,¹² U Müller-Ladner,⁸ DE Furst,¹³ A Tyndall,³ M Matucci-Cerinic,⁷
EUSTAR Group



Very early systemic sclerosis - diagnózis

- ☞ Raynaud phenomen
- ☞ Puffy fingers (sclerodactylia-ba forduló)
- ☞ Antinuclearis antitest +
- ☞ Specifikus SSc antitest + (anticentromer és antitopoisomerase-I - antiScl70)
- ☞ Kóros capillaroscopos kép - scleroderma pattern



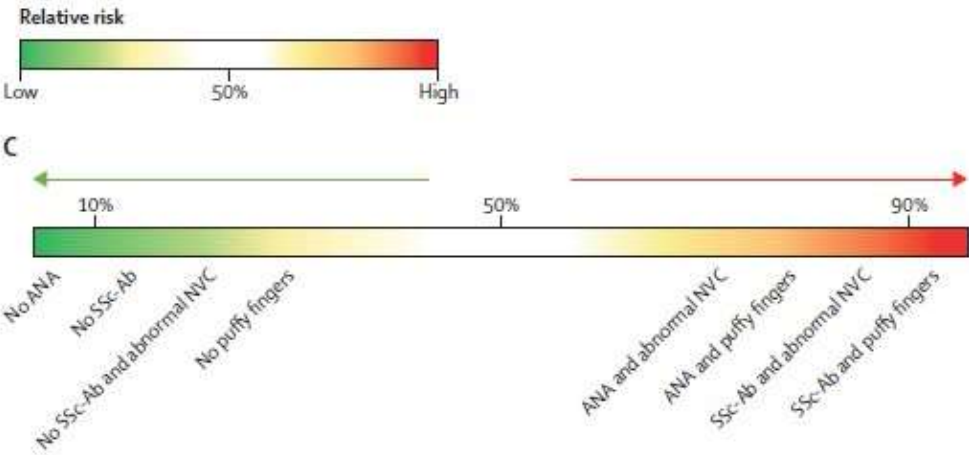
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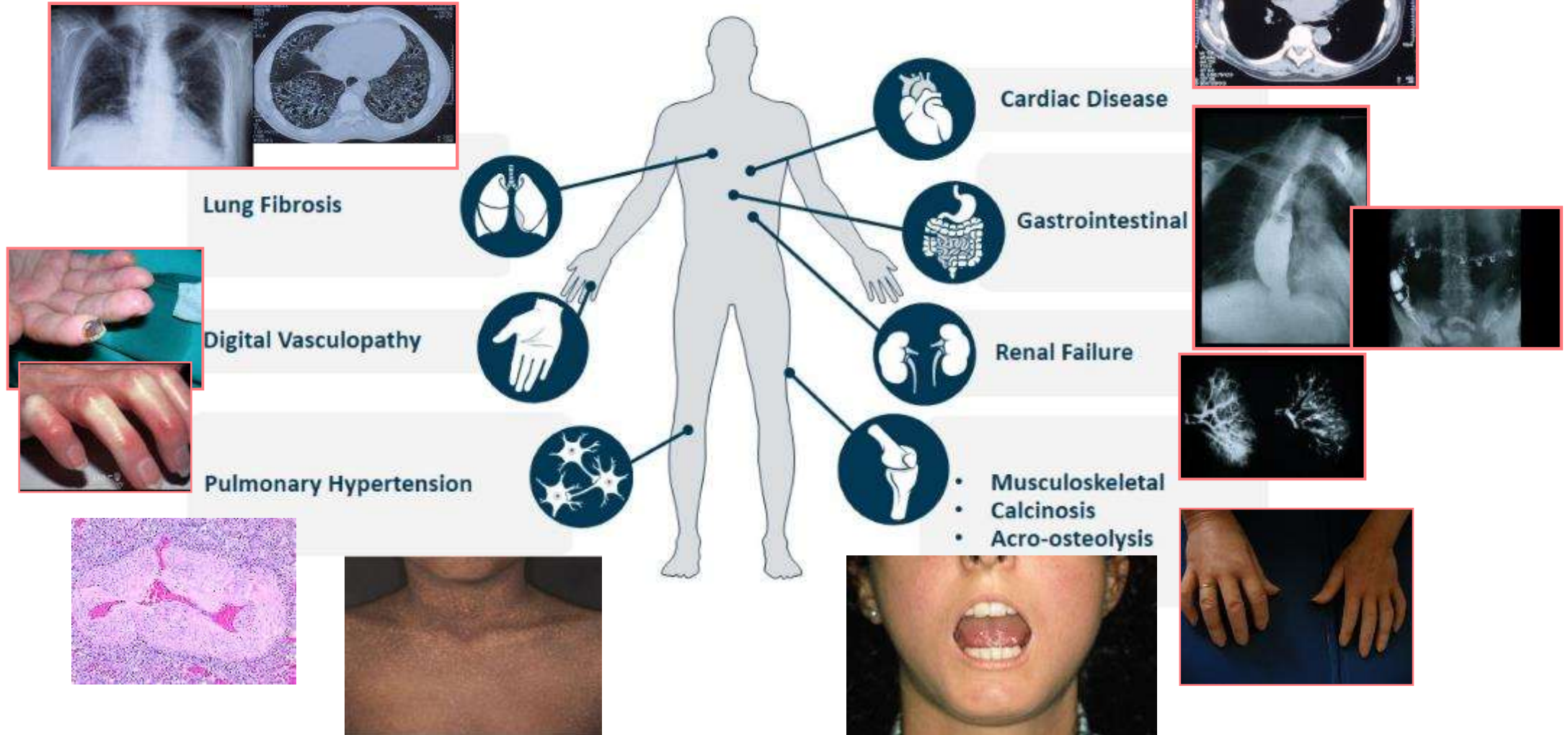
Progression of patients with Raynaud’s phenomenon to systemic sclerosis: a five-year analysis of the European Scleroderma Trial and Research group multicentre, longitudinal registry study for Very Early Diagnosis of Systemic Sclerosis (VEDOSS)
Lancet Rheumatol 2021; 3: e834–43)

Proportion fulfilling 2013 ACR-EULAR criteria		ANA	Ssc-Ab	SSc pattern on NVC	Puffy fingers
In the presence of	ANA	58.9%	70.2%	75.0%	79.0%
	Ssc-Ab	70.2%	70.2%	82.2%	94.1%
	SSc-Ab pattern on NVC	75.0%	82.2%	70.1%	69.2%
	Puffy fingers	79.0%	94.1%	69.2%	70.8%
In the absence of	ANA	10.8%	31.0%	40.4%	47.5%
	Ssc-Ab	31.0%	31.0%	41.9%	49.6%
	SSc-Ab pattern on NVC	40.4%	41.9%	41.5%	50.9%
	Puffy fingers	47.5%	49.6%	50.9%	47.9%



VEDOSS EUSTAR cohort:
Progresszió : oesophageal symptoms (HR 1.66)

Klinikai manifesztációk



2013 EULAR/ACR klasszifikációs kritériumok - SSc diagnózis – szenzitivitás javulása

Panel 1: Summary items from the 2013 American College of Rheumatology and European League Against Rheumatism criteria for the classification of systemic sclerosis*

Proximal skin involvement

- Skin thickening of the fingers of both hands, extending proximal to the metacarpophalangeal joints (sufficient criterion; score 9)

Skin thickening of the fingers (only count the higher score)

- Puffy fingers (score 2)
- Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints; score 4)

Fingertip lesions (only count the higher score)

- Digital tip ulcers (score 2)
- Fingertip pitting scars (score 3)

Telangiectasia (score 2)

Abnormal nailfold capillaries (score 2)

Pulmonary arterial hypertension or interstitial lung disease (maximum score of 2)

- Pulmonary arterial hypertension (score 2)
- Interstitial lung disease (score 2)

Raynaud's phenomenon (score 3)

Systemic sclerosis-related autoantibodies (maximum score of 3)

- Anti-centromere (score 3)
- Anti-topoisomerase I (score 3)
- Anti-RNA polymerase III (score 3)

*A total score of 9 is needed for a definite classification.

A szubklasszifikáció nem fedi le a SSc- spektrum különböző fenotípusait

Panel 2: Typical features of the major subsets of systemic sclerosis

Limited cutaneous systemic sclerosis

- Distal skin sclerosis
- Long history of Raynaud's phenomenon
- Late-stage complications frequent
- Pulmonary arterial hypertension and severe gut disease frequent and serious

Diffuse cutaneous systemic sclerosis

- Proximal limb or trunk involvement, with skin sclerosis
- Short history of Raynaud's phenomenon
- Increased risk of renal crisis and cardiac involvement
- High frequency of severe lung fibrosis

Sine scleroderma

- Raynaud's phenomenon
- Typical systemic sclerosis serology or capillaroscopic features
- No skin thickening
- Organ-based or other vascular manifestations

Systemic sclerosis overlap syndrome

- One of the three subsets together with clinical and investigational features of another autoimmune rheumatic disease

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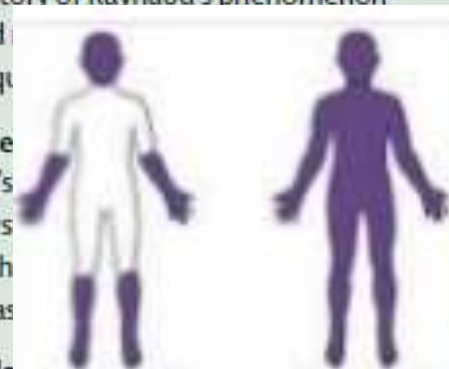
- Bőrtünetek kiterjedtsége
- Autoantitest profil
- Szervi érintettség
- Betegség progresszió és kimenetel

Diffuse cutaneous systemic sclerosis

- Proximal limb or trunk involvement, with skin sclerosis
- Short history of Raynaud's phenomenon
- Increased
- High frequency

Sine scleroderma

- Raynaud's
- Typical sys
- No skin th
- Organ-bas



Systemic sclerosis overlap syndrome

- One of the three subsets together with clinical and investigational features of another autoimmune rheumatic disease

SSc



SSc – Raynaud sy - DU



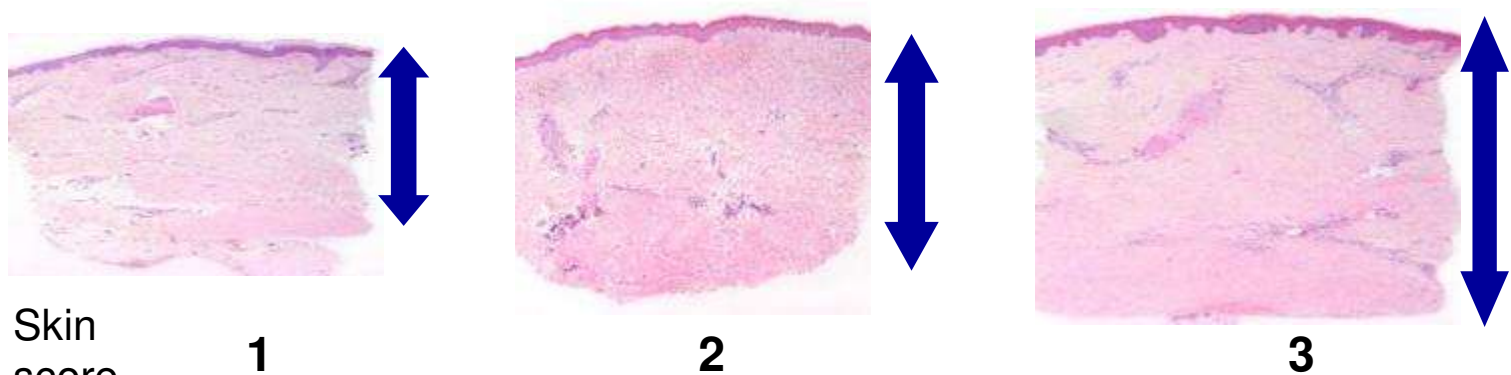
- DU: SSc-ban *kb. 50%-ban* alakulnak ki
- dcSSc-ben korábban jelennek meg, anti-Scl70 pozitívokban gyakoribb, gyakori asszociáció a CV eltérésekkel
- Szövődmények: infekció, gangraena, osteomyelitis, autoamputáció!

Genetic and environmental endogenous/exogenous risk factors, epigenetic mechanisms	Very Early microvascular morphological markers	Early microvascular morphological markers, very early fibrotic reaction, presence of serum autoantibodies	Increased microvascular morphological markers, specific autoantibodies, evident tissue fibrosis	Advanced microvascular morphological changes, increased tissue/organs fibrosis and specific autoantibodies	Microvascular failure and marked diffuse tissue/organs fibrosis with necrosis/failure
Normal	VERY EARLY	EARLY*	EARLY-ACTIVE	ACTIVE*	LATE*
Morphological capillaroscopic validated patterns *of progressive microvascular and tissue damage in systemic sclerosis corresponding to the pathophysiology					



Bőrtünetek vizsgálat

Modified Rodnan Skin Score (MRSS)



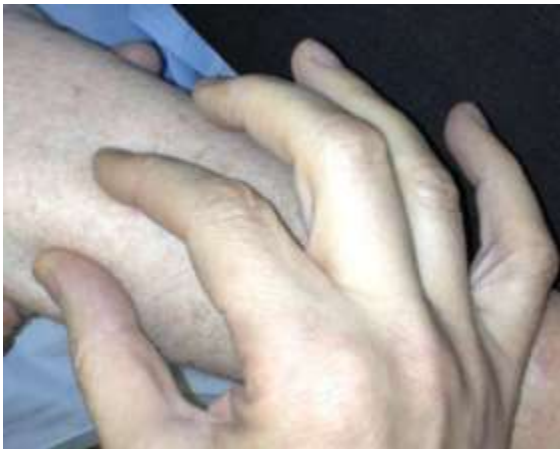
Skin score grade

1

2

3

Histological correlation of skin score



Calculating the MRSS

0
1
2
3

Uninvolved
Mild thickening
Moderate thickening
Severe thickening

Upper arm

Forearm

Hand

Fingers

Thigh

Leg

Foot

0 1 2 3

0 1 2 3

0 1 2 3

0 1 2 3

0 1 2 3

0 1 2 3

0 1 2 3

0 1 2 3

0 1 2 3

0 1 2 3

0 1 2 3

0 1 2 3

0 1 2 3

0 1 2 3

Face

Upper arm

Forearm

Hand

Fingers

Thigh

Leg

Foot

0 1 2 3

0 1 2 3

0 1 2 3

0 1 2 3

0 1 2 3

0 1 2 3

0 1 2 3

0 1 2 3

Chest

Abdomen

0 1 2 3

0 1 2 3

Date

ID

Total

/ 51



Standardization of the mRSS for use in clinical trials of SSc.
Khanna D, .. Denton CP. J Scleroderma Relat Disord. 2017;2:11-18.

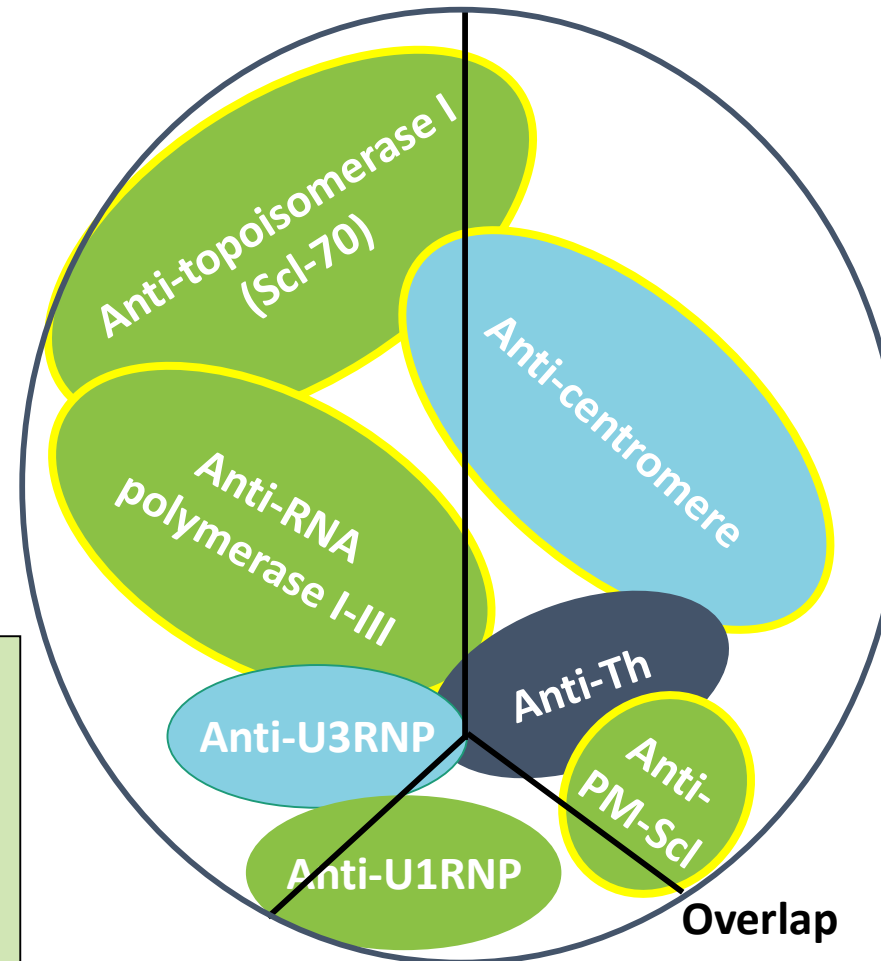
Szerológiai alcsoportok SSc-ben

Diffúz cutan SSc

Limitált cutan SSc

50-60%:

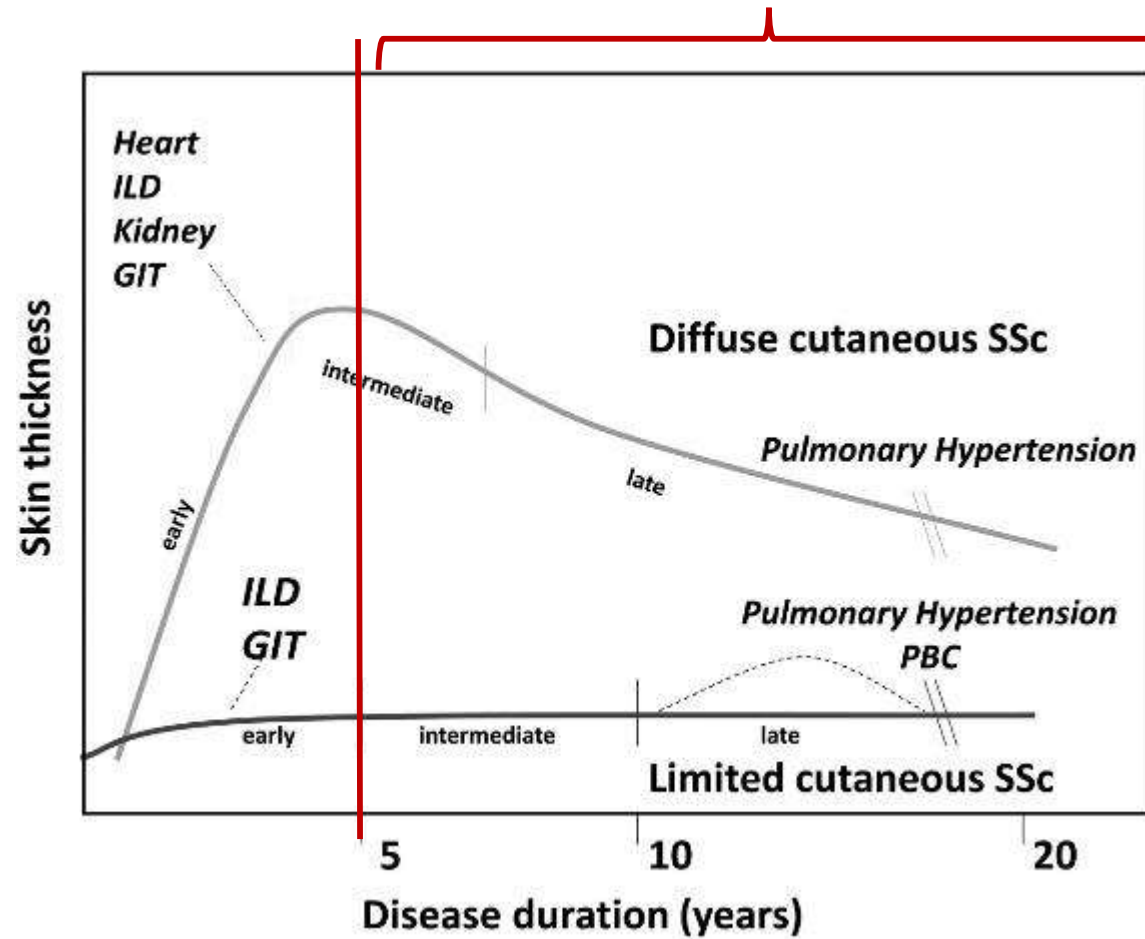
**anti-centromer,
anti-Scl70,
anti-RNA polimeráz III**



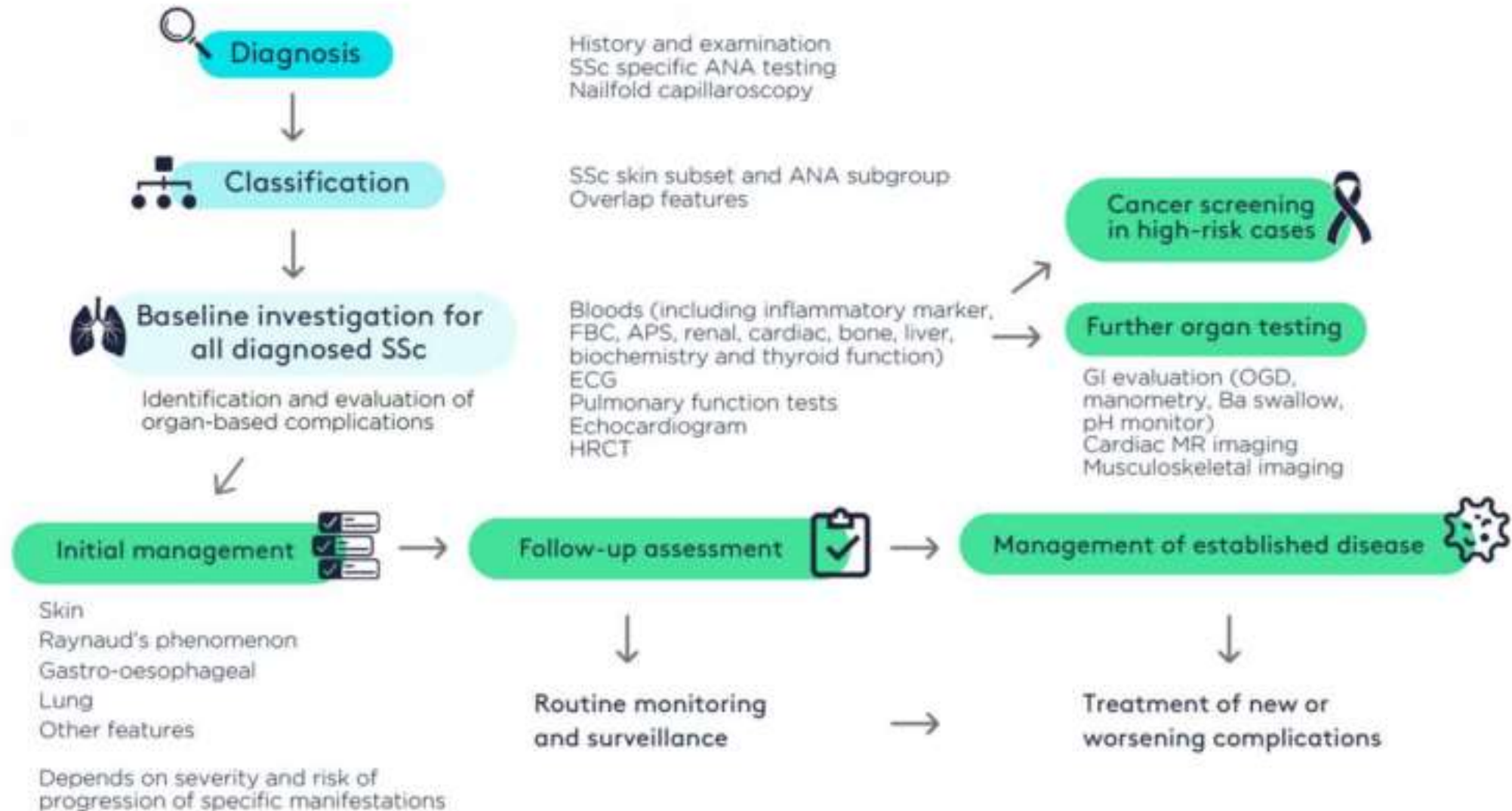
Anti- Scl-70 = ILD
Anti-centromere = PAH
Anti-RNA pol III = renalis crisis, malignitás, rapid bőr progresszió
Anti-PM-Scl = SSc-myositis
Anti-Ro52 – súlyosabb ILD
Anti-U3RNP = ILD, PAH, myositis
Anti-Th/To = ILD, PAH

Terápiás sürgősség – Korai
progresszorok

Hosszútávú progresszió és tartós tünetek



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



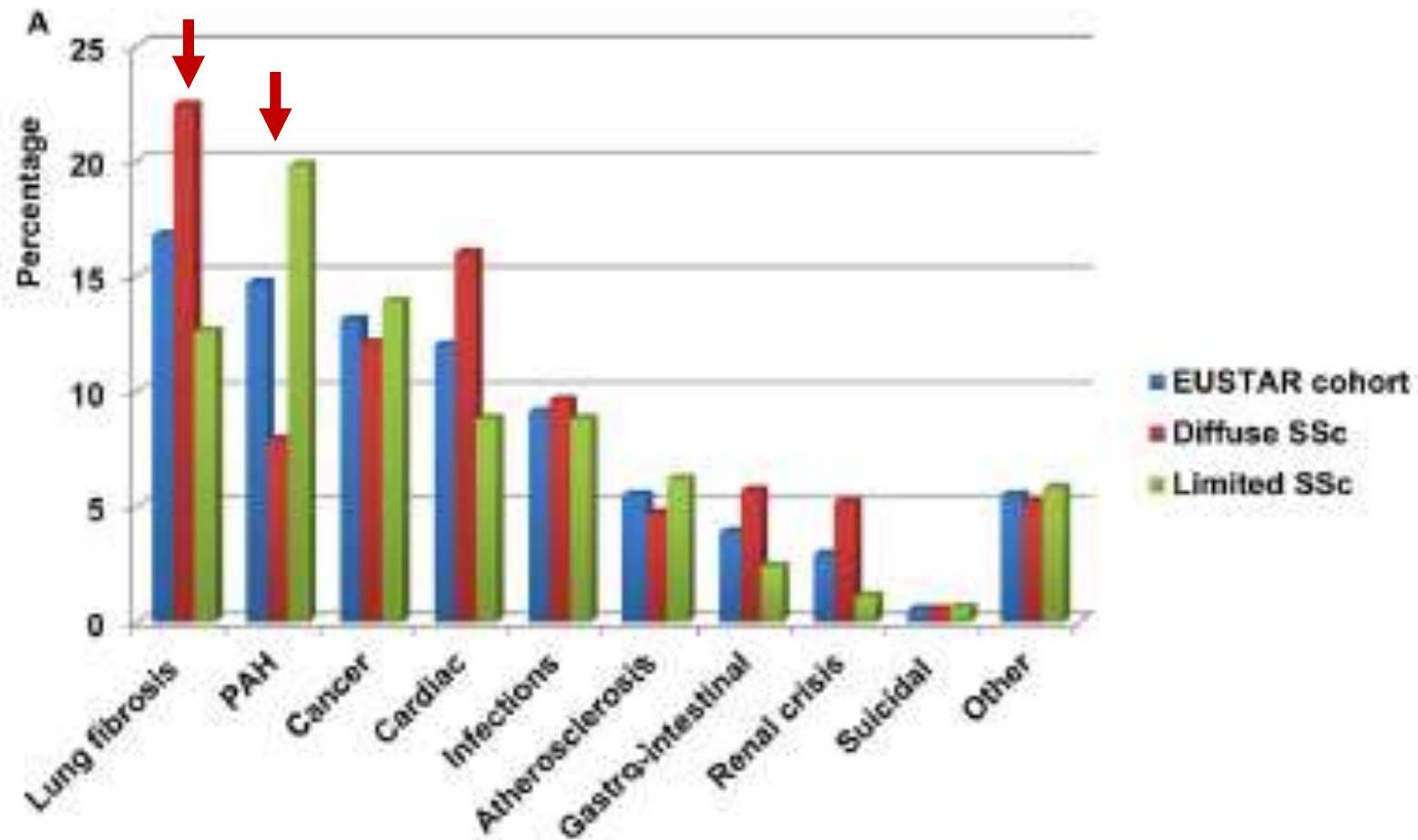


Figure 2 (A) Causes of death in the entire EUSTAR sample and in the limited and diffuse cutaneous forms. (B) Comparison of causes of death in the EUSTAR and in the death certificates samples. The results are presented as % of deaths. EUSTAR, European Scleroderma Trials and Research; PAH, pulmonary arterial hypertension; SSc, systemic sclerosis.



Contents lists available at ScienceDirect

Annals of the Rheumatic Diseases

journal homepage: <https://www.sciencedirect.com/journal/annals-of-the-rheumatic-diseases>

Version of Record

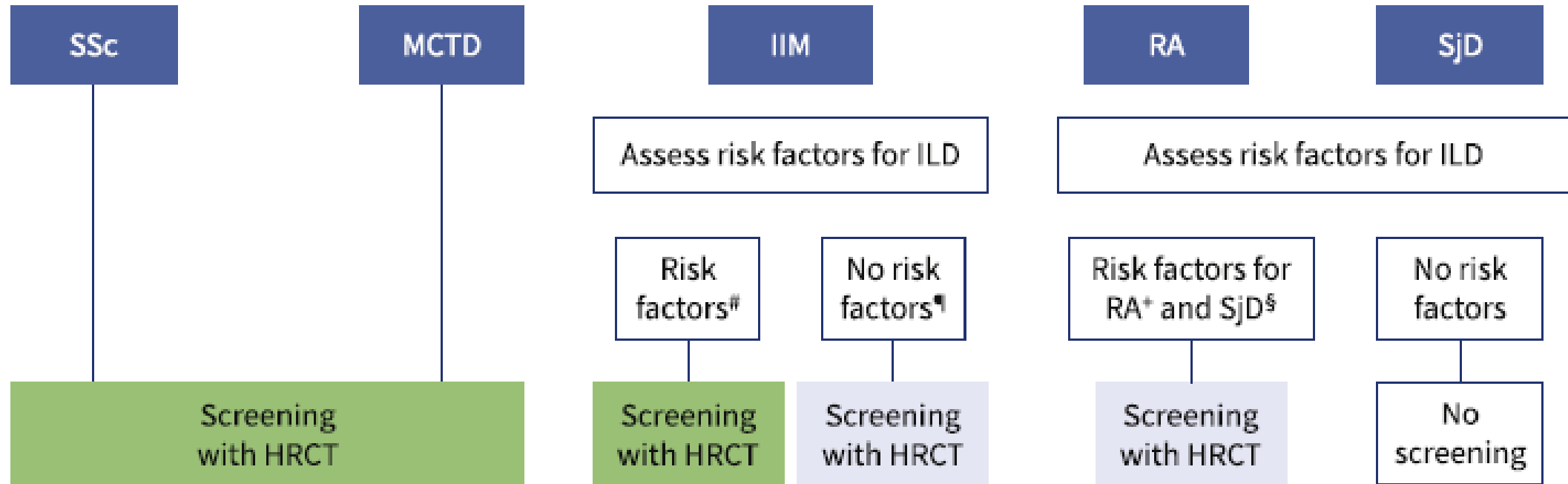
ERS/EULAR clinical practice guidelines for connective tissue diseases associated interstitial lung disease

Katerina M. Antoniou^{1,36}, Oliver Distler^{2,36}, Ana-Maria Gheorghiu³,

Table 3
Risk factors in patients with connective tissue disease and rheumatoid arthritis (RA) defining an at-risk patient population that should be screened for interstitial lung disease

	SSc	RA	IIM	SjD
Demographics	• Longer disease duration	• Older age • Male sex • Smoking	• Older age	• Older age • Male sex
Circulating markers	• Increased KL-6 • Presence of ATA-I	• Increased ESR • Presence of anti-CCP, RF	• Increased CRP, ESR • Presence of anti-Jo1, anti-MDA-5, anti-Ro52	• Increased CRP • Presence of anti-Ro52
Extrapulmonary involvement	• Diffuse cutaneous SSc • Higher mRSS	• Higher articular disease activity	• Anti-synthetase syndrome • Clinical amyopathic dermatomyositis • Skin involvement[#] • Arthritis/arthritis	• Presence of extrapulmonary involvement

Screening of CTD for ILD



Consider in every patient:

- Assessment of respiratory symptoms
- Lung function tests (FVC and D_{LCO}) in case of symptoms or CT abnormalities

Strong recommendation

Conditional recommendation

Clinical practice

Table 4
Risk factors for poor outcome, defined as disease progression and death, in patients with connective tissue disease (CTD)-associated interstitial lung disease (ILD) and rheumatoid arthritis (RA)-associated ILD

	SSc [#]	RA [#]	IIM ^{#,†}
Demographics	• Older age • Male sex • African American ethnicity	• Older age at RA onset • Male sex	
Circulating markers	• Elevated ESR, CRP • ATA-I	• Anti-CCP, RF	• Elevated ferritin • Anti-MDA-5, anti-synthetase
Pulmonary function/markers	• Baseline PFTs (FVC, D_{LCO})	• Baseline PFTs (low FVC and/or D_{LCO})	
Imaging/histology	• Higher extent of ILD on HRCT	• UIP and probable UIP HRCT/histological patterns • Higher extent of ILD on HRCT	• Higher extent of ILD on HRCT and ILD pattern on HRCT
Extrapulmonary involvement	• Recent onset of SSc with rapid skin progression, more extensive skin fibrosis (mRSS)	• Higher articular disease activity	

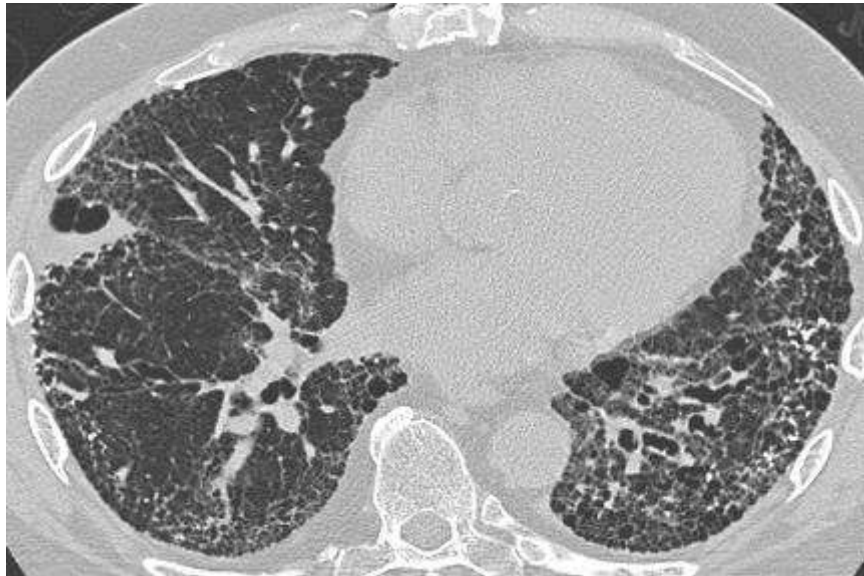
Progresszió megítélése és monitorozás



	igen	nem
HRCT kiterjedés	>20%	<10%
FVC kiindulás	<normál	normál
Dlco kiindulás	<normál	normál
FVC változás 12 hónap	≥ 10%	<5%
Dlco változás 12 hónap	≥ 15%	<15%
Tünetek	igen	nem
Akut kezdet	igen	nem
CTD-ILD beteg monitorozása	FVC és Dlco - Alacsony rizikó esetén 6 havonta - Magas rizikó esetén 3 havonta	
	HRCT - Alacsony rizikó esetén 24 havonta - Magas rizikó esetén 12 havonta	
	Új légzőszervi panasz Azonnali vizsgálat!	

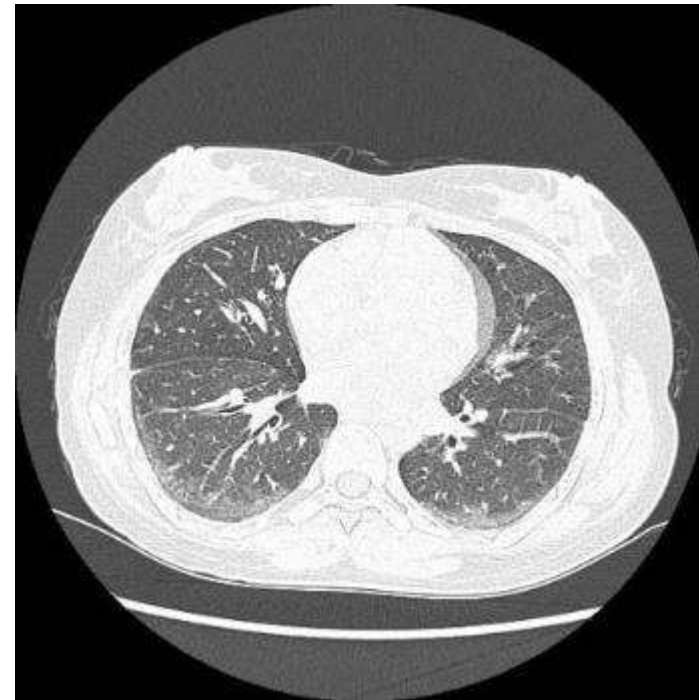
- **Tüdő HR-CT**
- - **Technikai nehézségek**
 - **Kiértékelés nehézségei**

UIP pattern



https://en.wikipedia.org/wiki/Usual_interstitial_pneumonia

NSIP pattern



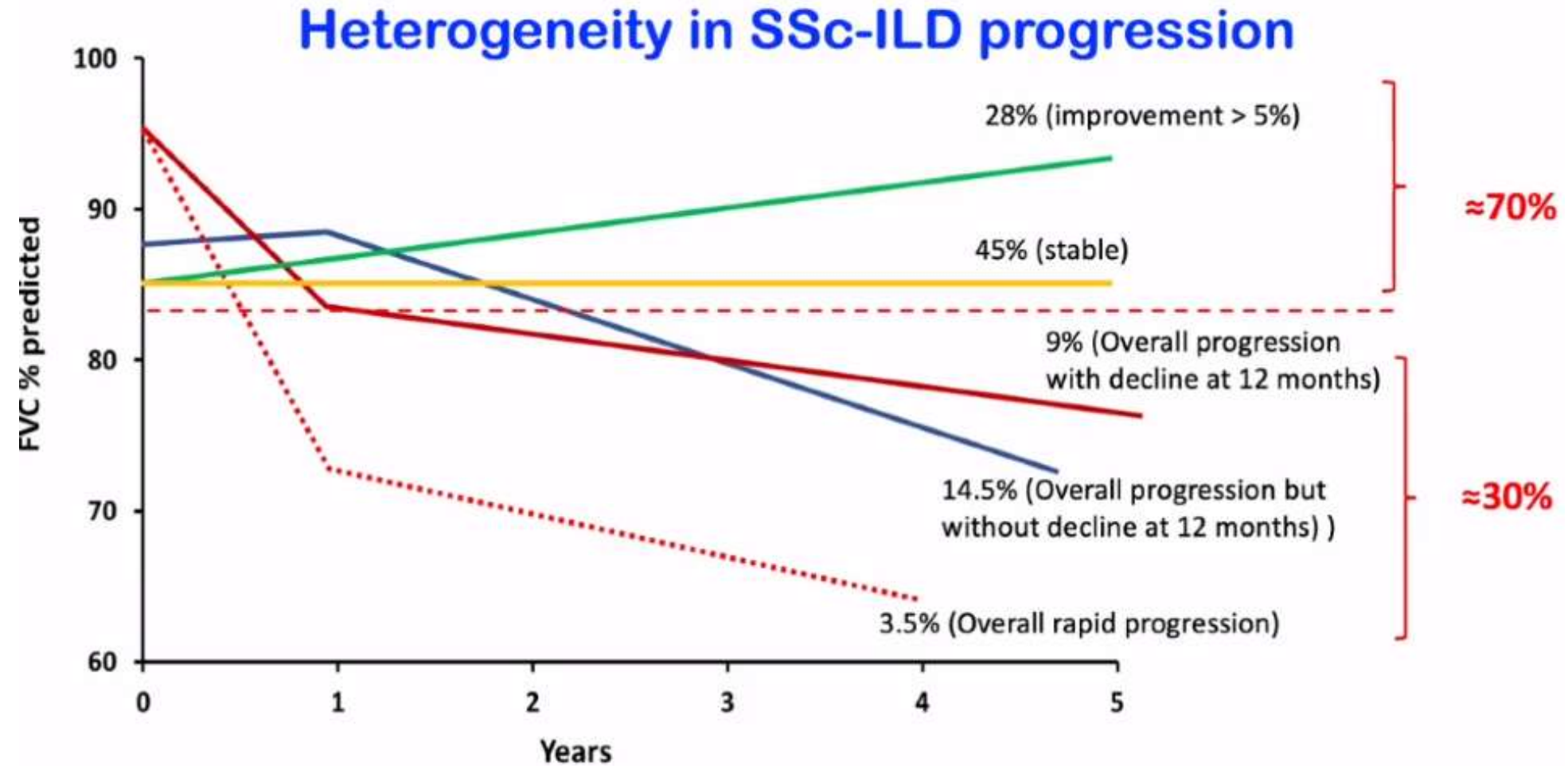
<https://radiopaedia.org/articles/non-specific-interstitial-pneumonia-1?lang=us>

SSc-ILD monitoring

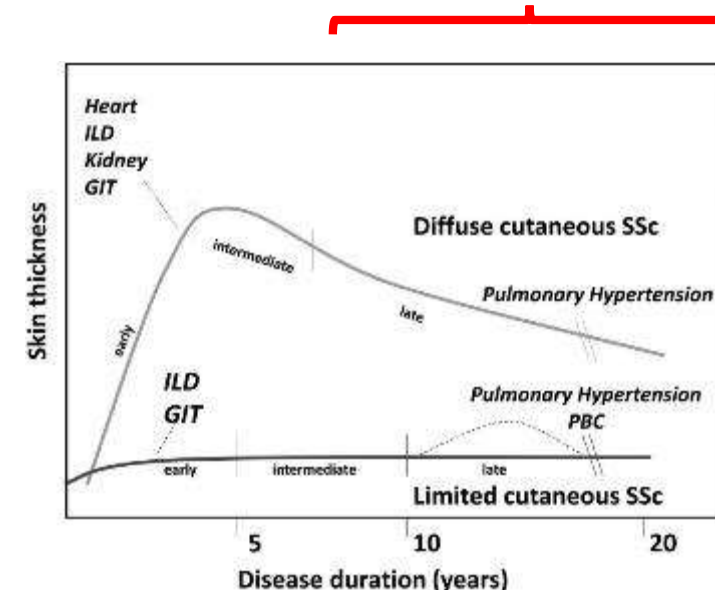
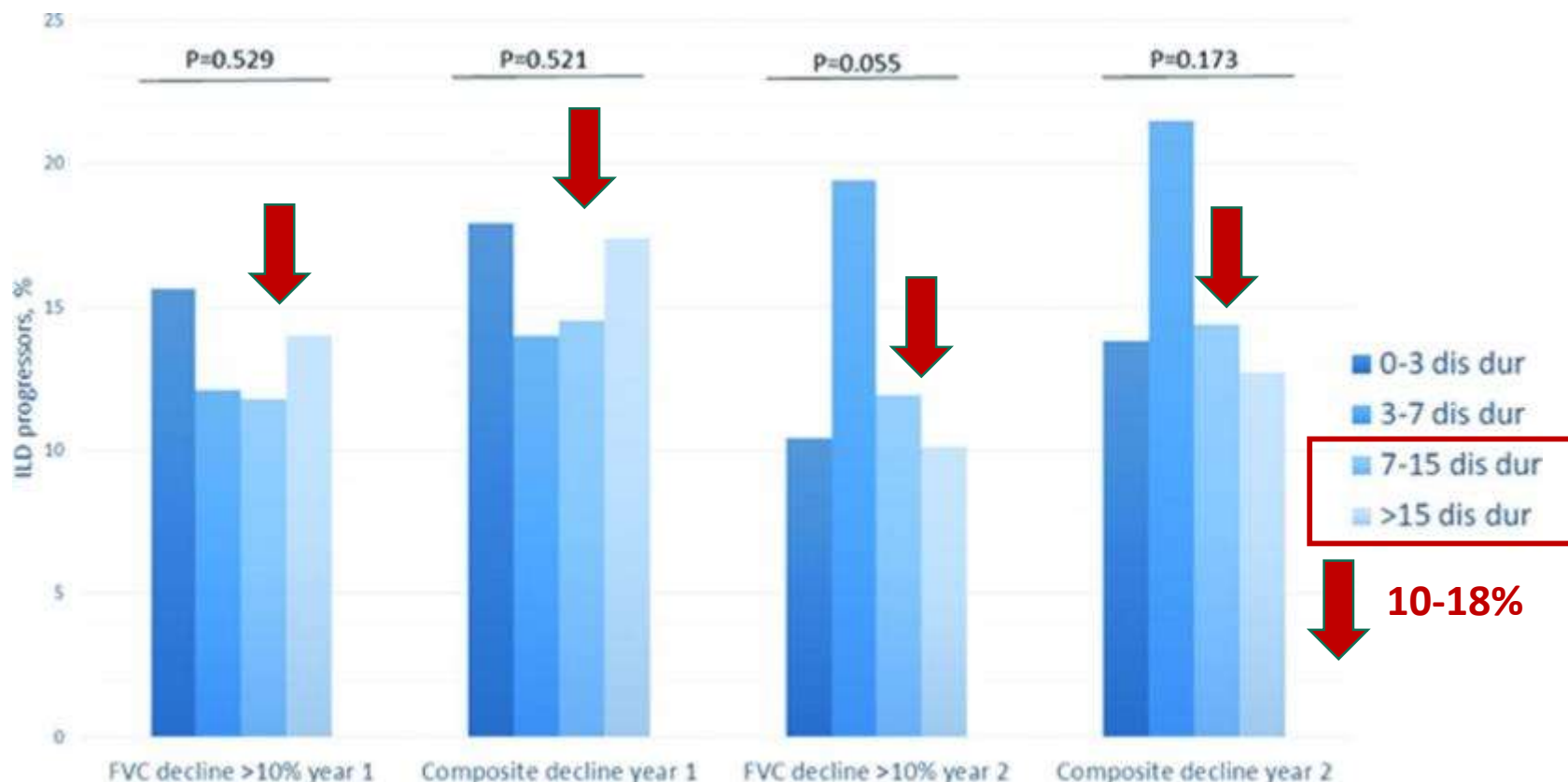
	Assess prognosis, risk of progression and disease severity at every visit				
	High risk		Low risk		Indication of progression
Disease duration	<3–5 years	>3–5 years	<3–5 years	>3–5 years	Anytime
Lung function test (FVC and D_{LCO})	Every 3–6 months	Every 6–12 months	Every 6–12 months	Every 12 months	Conduct
HRCT (pattern and extent)	Every 12 months	Every 12 months	After 2 years	Clinical indication	Conduct
6MWD and O ₂ desaturation	Every 6–12 months	Every 6–12 months	Every 12 months	Every 12 months	Conduct
Patient-reported outcome measures	Every 6–12 months	Every 6–12 months	Every 12 months	Every 12 months	Conduct

Conditional recommendation
 Usual clinical practice

EUSTAR database



FVC decline >10% and composite FVC and DLCO decline in the first and second 12+/-3 months within the four subgroups segregated by disease duration.



2258 SSc-ILD beteg

Betegség fennállási idő: (20.8%) ≤3 év, 550 (24.4%) >3- ≤7 év, 752 (33.3%) >7- ≤15 év, 488 (21.6%) >15 év



ILD team

Alapbetegség diagnózisának felállítása (Alcsoport besorolás)

ILD szűrővizsgálatok

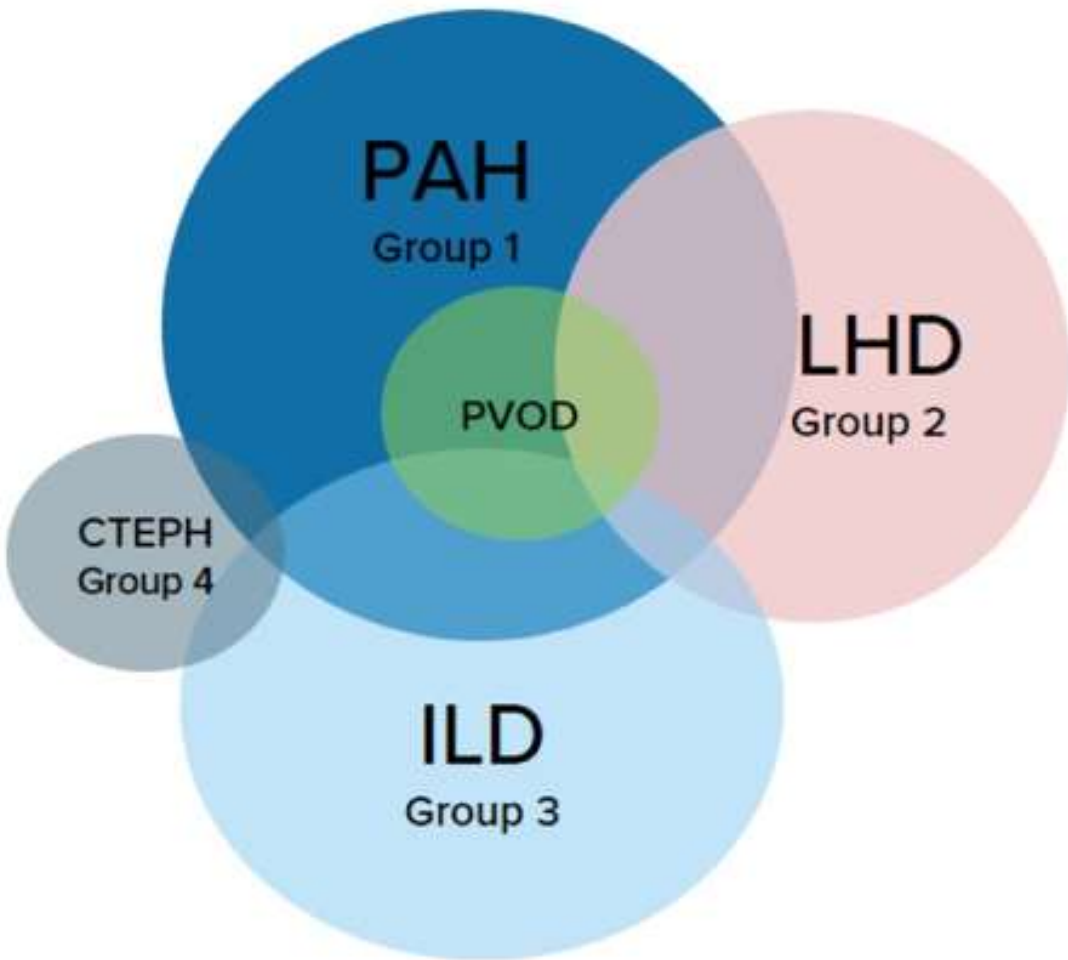
Progresszív ILD predikciója

Vizsgálatok a követés során

(klinikai tünetek, légzésfunkció, képalkotó)

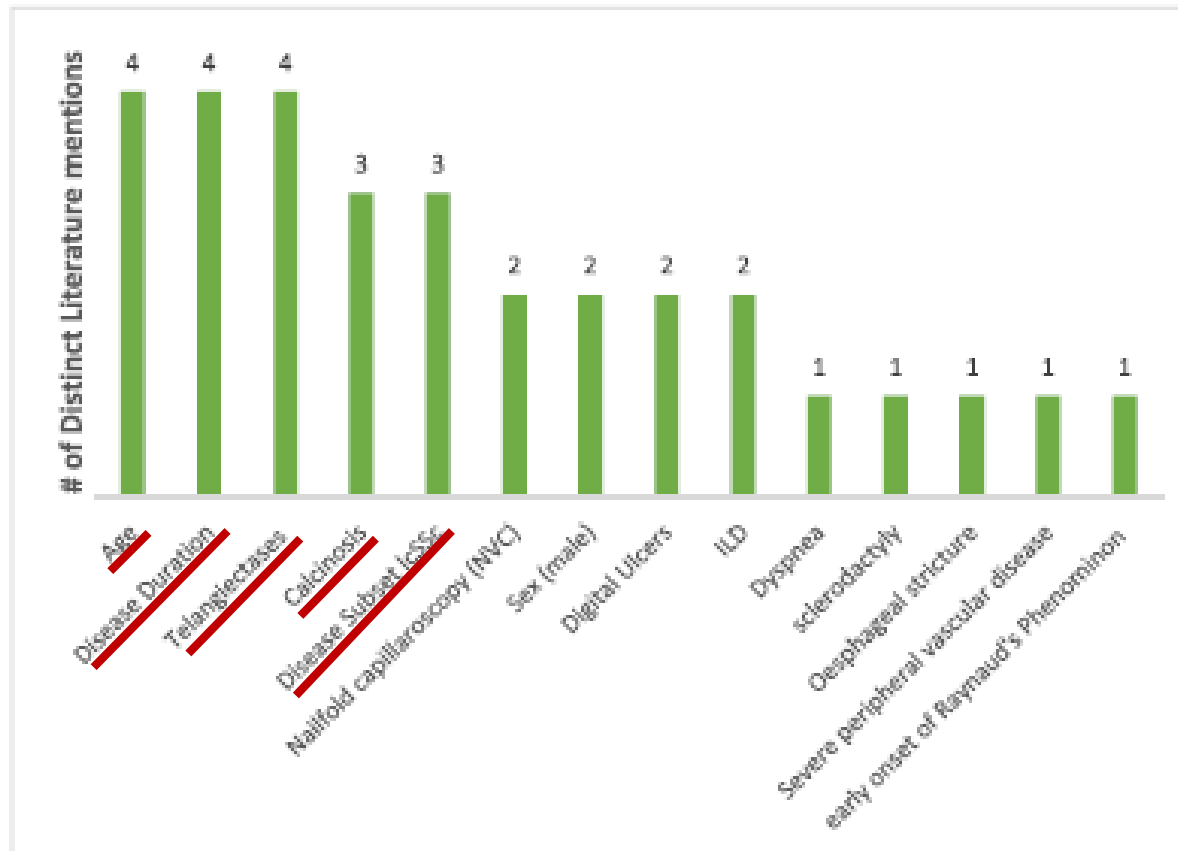
Terápia tervezése - gyógyszerválasztás

PAH fenotípusok SSc-ben

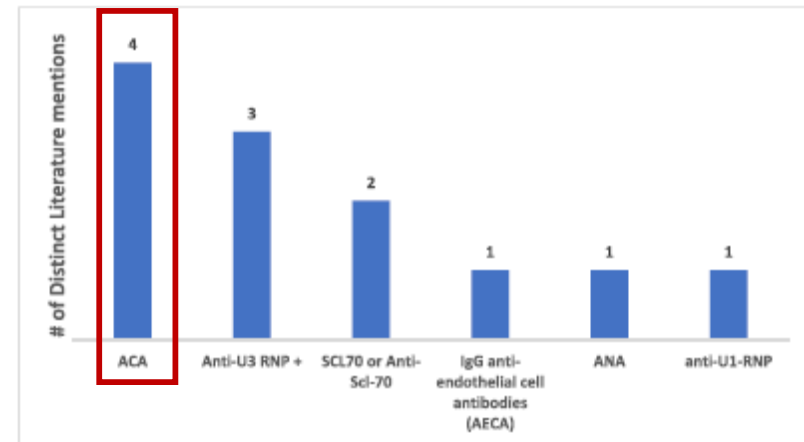


Pre-capillary PH	Mean PAP > 20 mmHg <i>plus</i> PAWP ≤ 15 mmHg <i>plus</i> PVR > 2 Wood units
lpcPH	Mean PAP > 20 mmHg <i>plus</i> PAWP > 15 mmHg <i>plus</i> PVR ≤ 2 Wood units
CpcPH	Mean PAP > 20 mmHg <i>plus</i> PAWP > 15 mmHg <i>plus</i> PVR > 2 Wood units
PH due to chronic lung disease	Severe PH: PVR ≥ 5

SSc-PAH



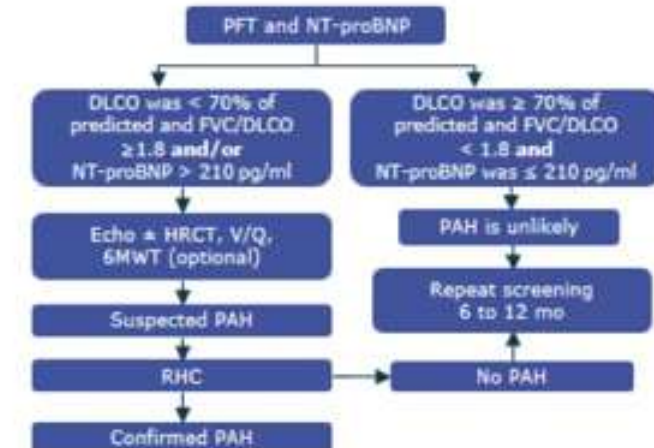
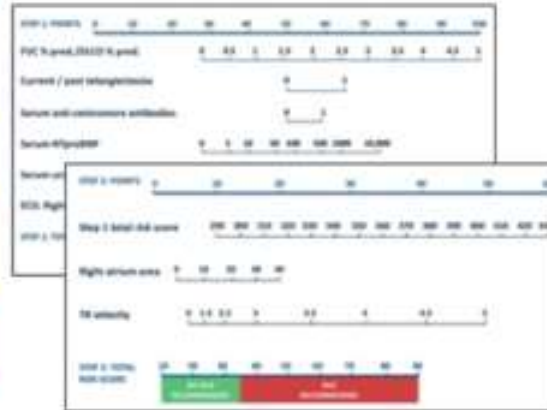
c. Patient characteristics associated with SSc-PAH as reported in literature



d. Antibody profiles associated with SSc-PAH as reported in literature

SSc-PAH szűrése

Peak TRV, m/s	Presence of other echocardiographic PH signs	Echocardiographic probability of PH
≤ 2.8 or not measurable	No	Low
≤ 2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
> 3.4	Not required	



Echo^[a] (TTE)

ESC/ERS 2015 guidelines recommend the use of annual resting TTE as a screening test in asymptomatic patients with SSc and in symptomatic patients with other CTDs

DETECT^[b]

A 2-step algorithm using nonechocardiographic and echocardiographic variables to screen for PH

Delphi-based expert consensus^[c]

Consensus on strongly suggested and easily applicable tools for annual systemic assessment of organ involvement in SSc

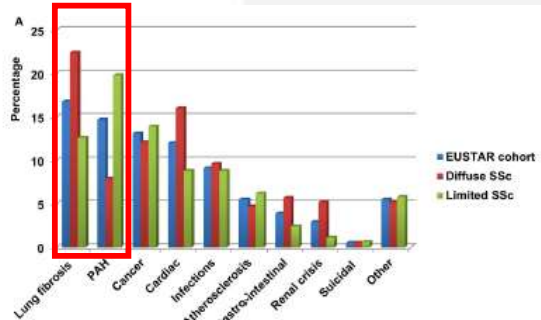
Australian Scleroderma Interest Group^{[d][e]}

An Australia-wide screening program where enrolled patients were recommended to have PFTs, EKG, TTE, and NT-proBNP measurement; and if abnormal, RHC and 6MWD

SSc-ILD, SSc-PAH

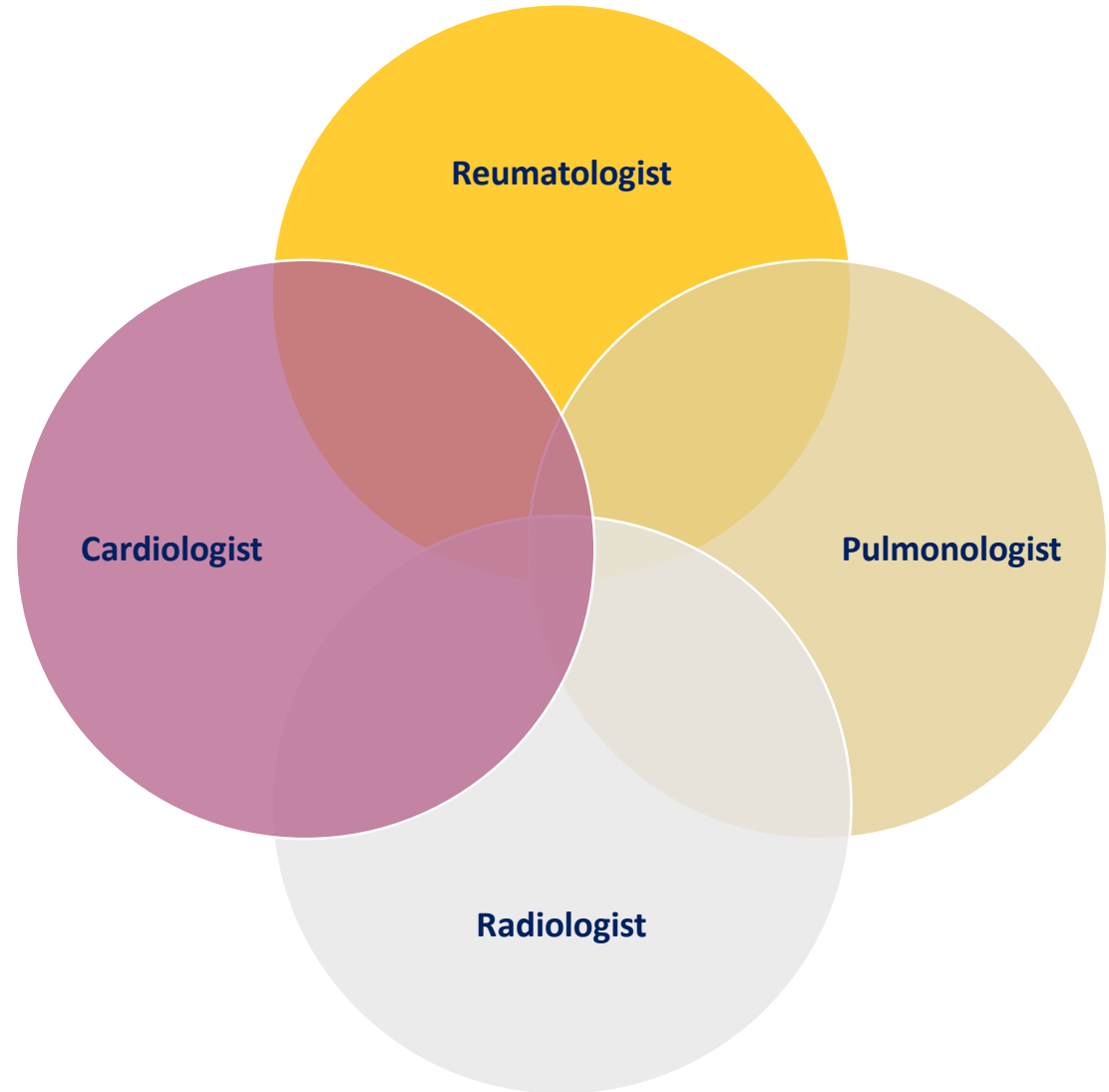
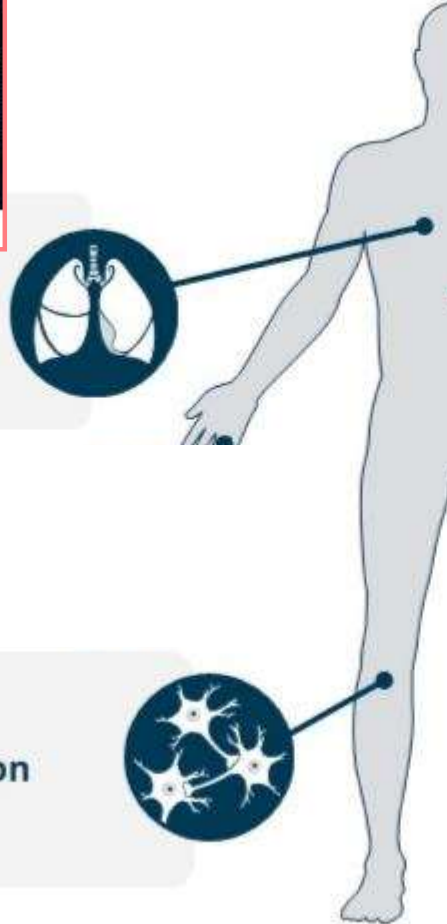
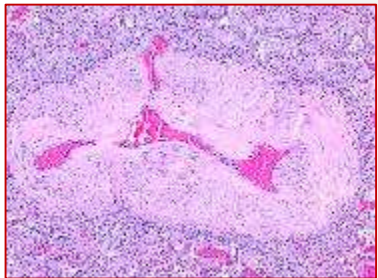


Lung Fibrosis



Ann Rheum Dis 2017;**76**:1897–1905.

Pulmonary Hypertension



Assessment of myocardial fibrosis and microvascular damage in systemic sclerosis by magnetic resonance imaging and coronary angiotomography

Tatiana S. Rodríguez-Reyna¹, Martha Morelos-Guzmán², Pablo Hernández-Reyes³, Karla Montero-Duarte², Cynthia Martínez-Reyes¹, Carlos Reyes-Utrera¹, Jorge Vázquez-La Madrid², Jaime Morales-Blanchir¹, Carlos Núñez-Alvarez² and Javier Gábledes-Contreras^{1,4}

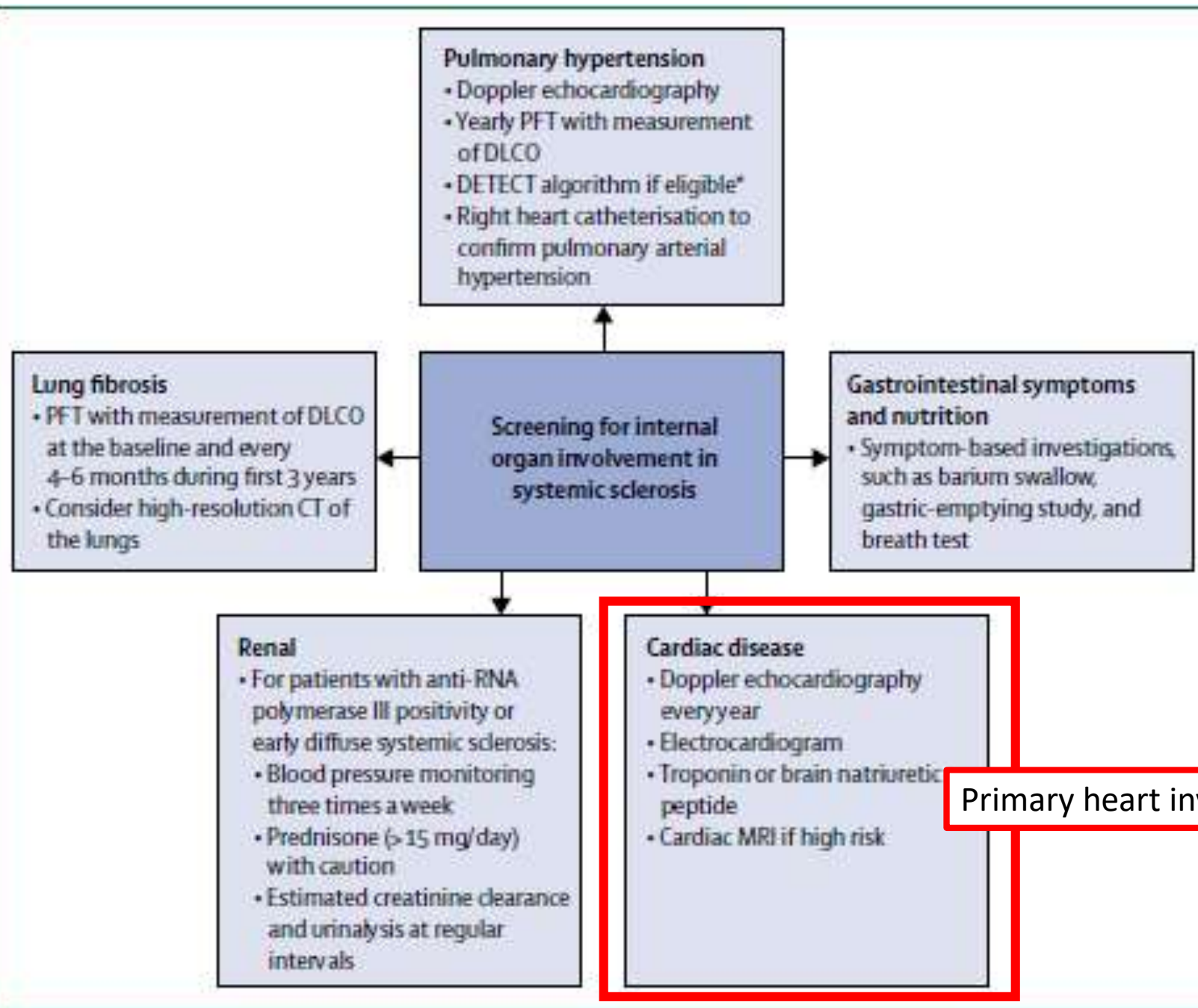


FIG. 3 Cardiac MRI in T1 gradient echo/echo planar imaging pulse sequence showing a diffuse subendocardial perfusion defect in the left ventricle wall of a SSc patient

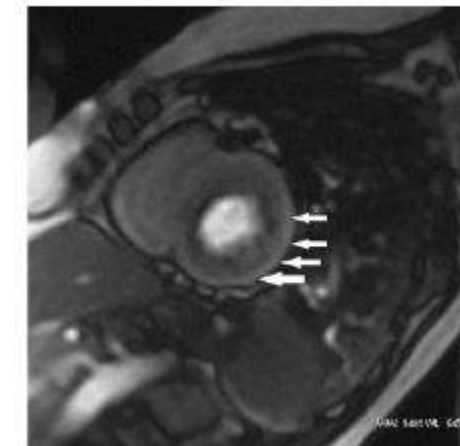
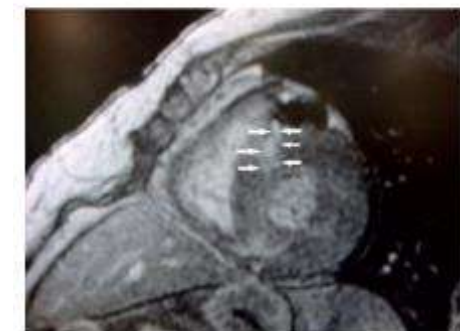
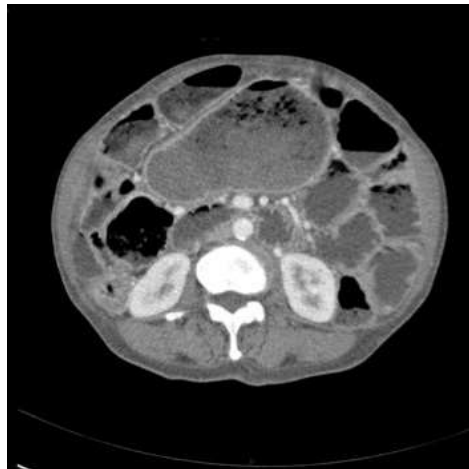
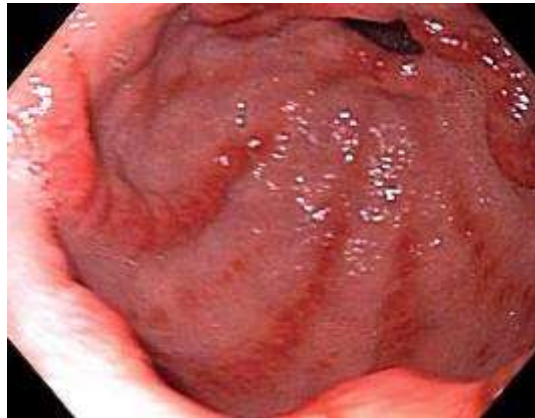


FIG. 2 Cardiac MRI in T1 gradient echo sequence showing late enhancement in the anteroseptal wall of the left ventricle of a SSc patient



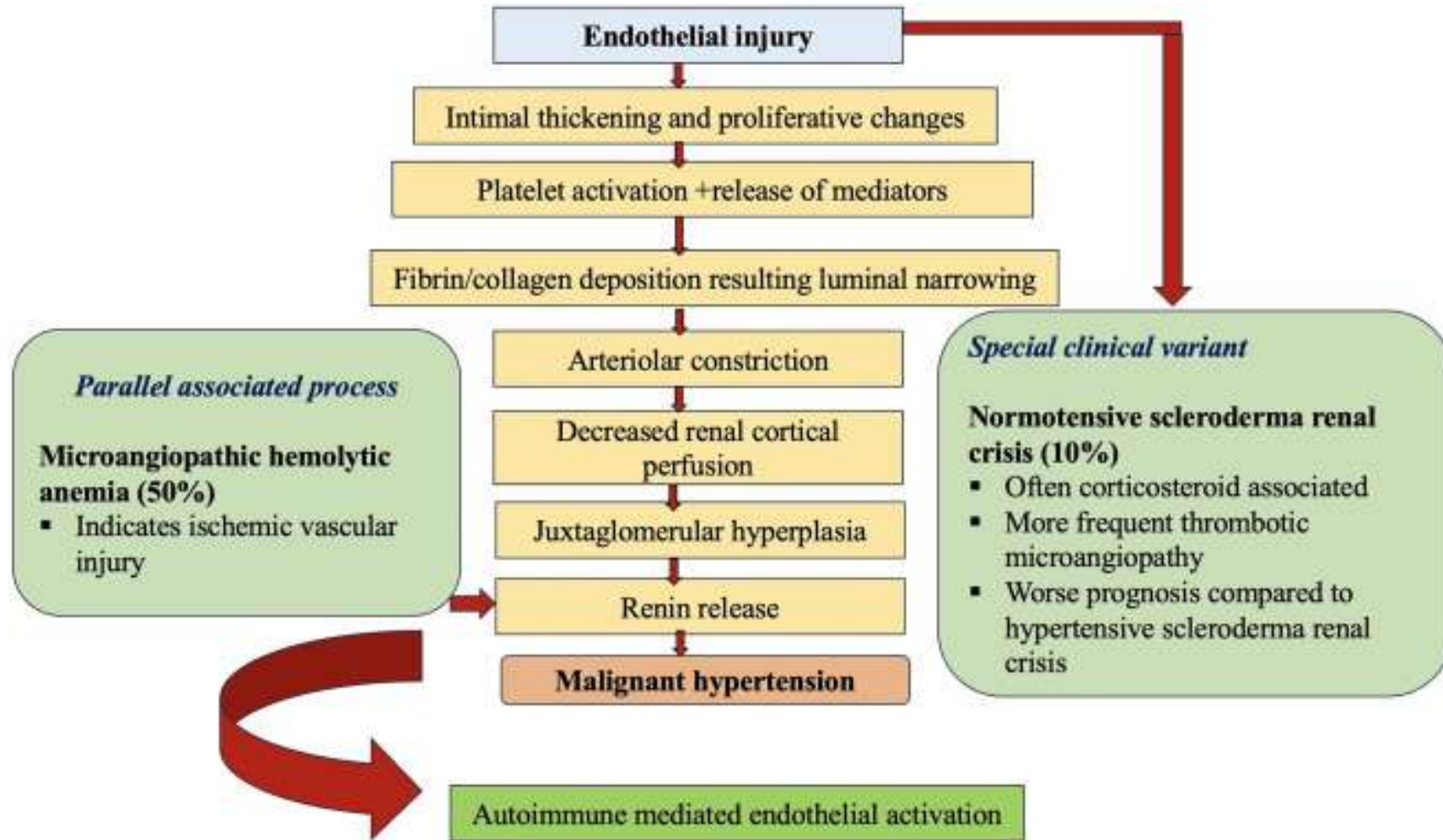
Gasztrointesztinális érintettség

- A betegek 90%-ában
- Patogenetika: fibrosis, autonóm neuropathia, vascularis malformációk
- Érintett szakasz: oesophagus, de a GI traktus bármelyik része
- Nyelőcső dysmotilitás, szűkület-tágulat, reflux oesophagitis, „görögdinnye” gyomor, intestinalis pseudo-obstrukció, bakteriális túlnövekedés, anorectalis inkontinencia, exokrin pancreas insufficiencia



Veseérintettség

- Scleroderma renalis krízis: az SSc-s betegek 2-15%-a, dcSSc-ben az első 3-5 évben gyakoribb



Musculoskeletális tünetek



- 46-97%-ban
- Érintett területek: bőr és subcutis, ízületek, inak, vázizomzat, csontok
- Kontraktúrás ízületek, arthralgia, arthritis, tendinitis, crepitatio az ín felett („tendon friction rubs”), myalgia, myositis



Global management of systemic sclerosis – treatment considerations

Neurological

Neurological complications of SSc require multi-speciality management with careful exclusion of other relevant causes. 1C
Peripheral Sensory neuropathy of the feet is common. 2C

ILD

MMF is recommended as first line treatment with rituximab or cyclophosphamide i.v. as alternative. 1B
Consider adding rituximab or tocilizumab to MMF for progressive disease. 2C
Nintedanib recommended for progressive pulmonary fibrosis. 1B

PAH

PAH diagnosis by right heart catheter and treatment 1A initiated by a designated Pulmonary Hypertension Centres. 1B
Anticoagulation is not recommended in PAH-SSc. 1B

Renal

ACEi should be used in all cases of diagnosed SRC. 1A
Glucocorticoid treatment avoided in adult SSc due increased SRC risk. 1A
Renal biopsy should be considered when diagnosis uncertain. 1C
Referral for renal transplantation in cases without significant renal recovery. 1B

Skin

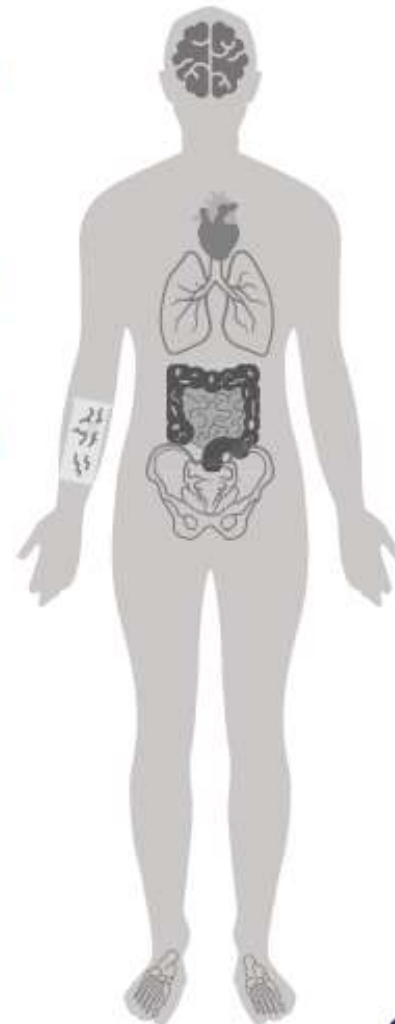
MMF is first line treatment for skin fibrosis in dcSSc. 1C
Antihistamines are often used for itch. 2C
Options for telangiectasia include skin camouflage, pulsed dye laser or intense pulsed light therapy. 2C

Musculoskeletal

Musculoskeletal manifestations of SSc may benefit from immunomodulatory treatments given for other complications. 1C

Digital ulcers

Severe digital vasculopathy with new tissue necrosis or critical ischaemia requires urgent clinical assessment. 1C
Sildenafil (or tadalafil) as 1st line agent in DU healing and secondary prevention and bosentan as second line treatment. 1C
Expert opinion supports use of IV prostanooids in promoting DU healing. 1C



Fatigue and Health related Quality of Life

Physical and occupational therapy may improve quality of life, pain, and fatigue. 2C

Cardiac

Immunosuppression with MMF for SSc- pHI when investigation suggests myocardial inflammation. 2C
Glucocorticoids and other bDMARDs may be added if appropriate and/or cyclophosphamide. 2C

Gastrointestinal

PPI and/or H2 receptor antagonists for reflux. 1C
Parenteral nutrition for severe malnutrition. 1B
Intermittent or rotational antibiotics SIBO. 2B
Anti-diarrhoeal agents or laxatives. 2B
Surgical intervention should be avoided. 1C

Reproductive health

Sexual dysfunction needs engagement of gynaecology, urology, and sexual health clinical services. 1C
For planned pregnancy in SSc identify significant organ dysfunction and discontinue harmful medication. 1C
Pregnancy management requires integrated multi-disciplinary care. 2C

Raynaud's phenomenon

Calcium channel blockers and other vasodilators may be considered in management of SSc-RP. 1B
Expert opinion suggests that PDE5i are effective as 2nd line agent for refractory SSc-RP. 1B
For rescue therapy in severe SSc-RP IV prostanooids may be considered. 1C

KEY:



Life-threatening complications



Non-lethal morbidity that has major impact on people with SSc

Szisztémás sclerosis

Patogenezis



Tünetek

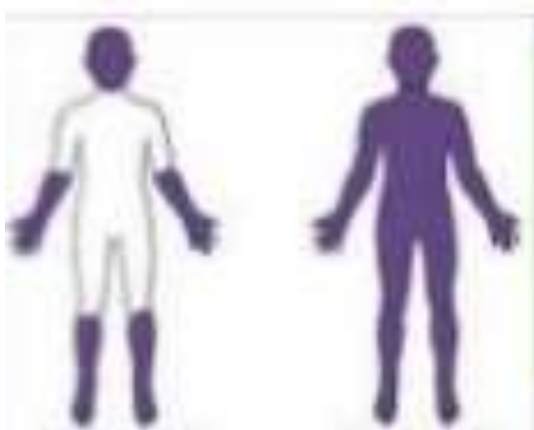


Diagnosztika



Terápia

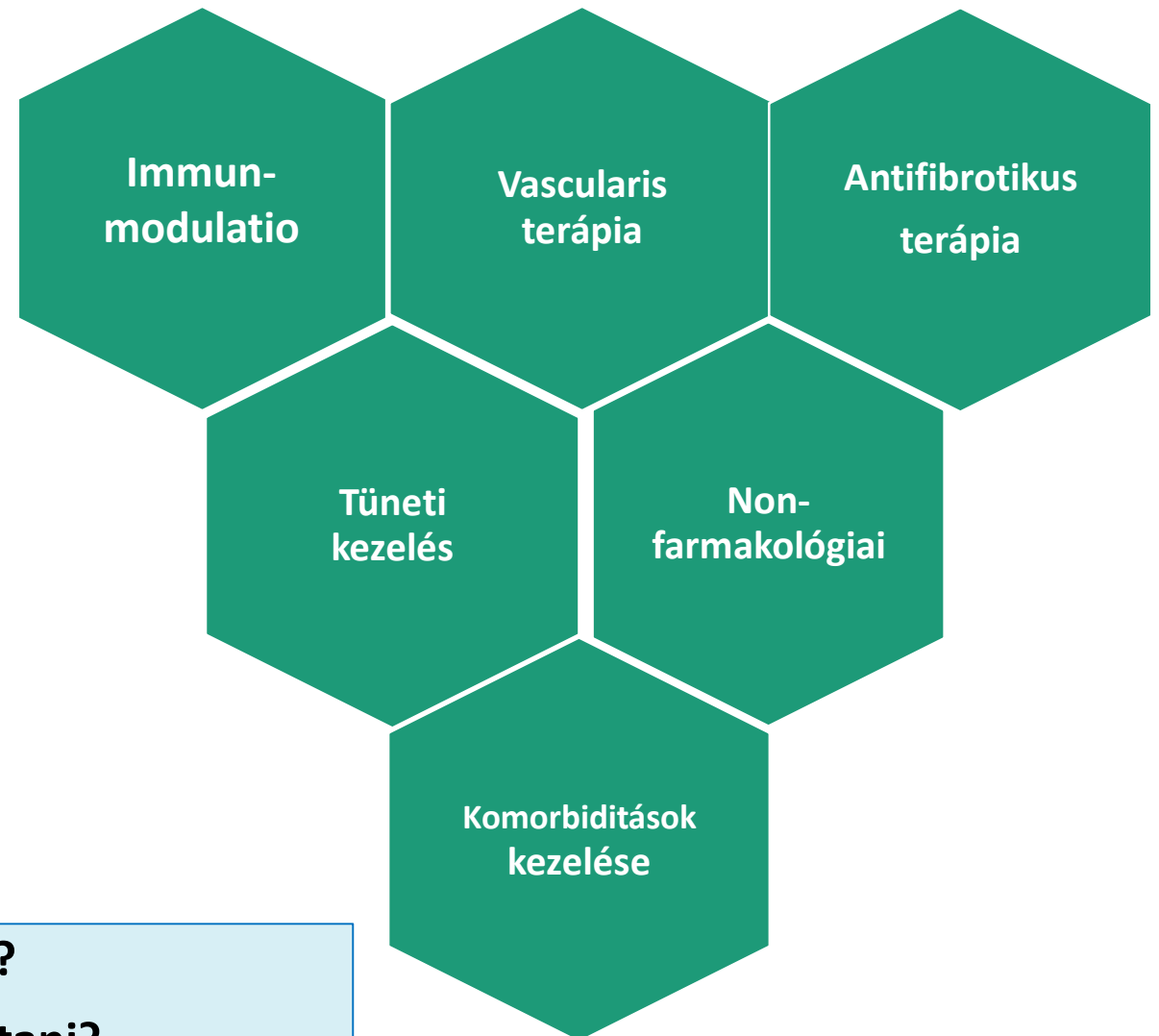
- Bőrtünetek kiterjedtsége
- Autoantitest profil
- Szervi érintettség
- Betegség progresszió és kimenetel



Lancet. 2017 Oct 7;390(10103):1685-1699

- Kit kell kezelni?
- Mikor kell indítani?
- Milyen terápiát?
- Meddig?

SSc- menedzsment



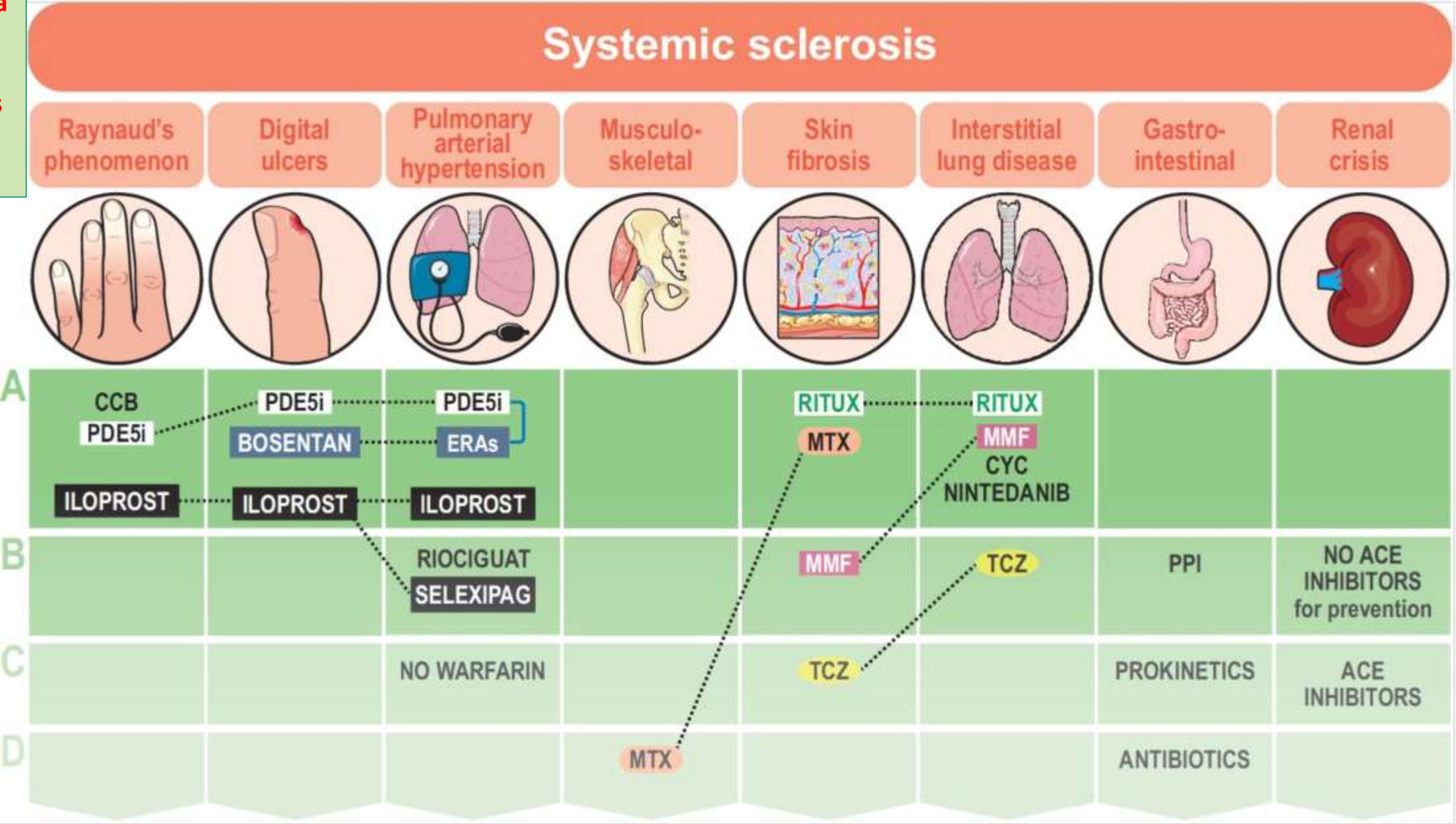
Kezelés:

Vascularis terápia

Immunszuppr./
Immunmoduláns

Antifibrotikus

SSc terápiás ajánlás – EULAR 2023



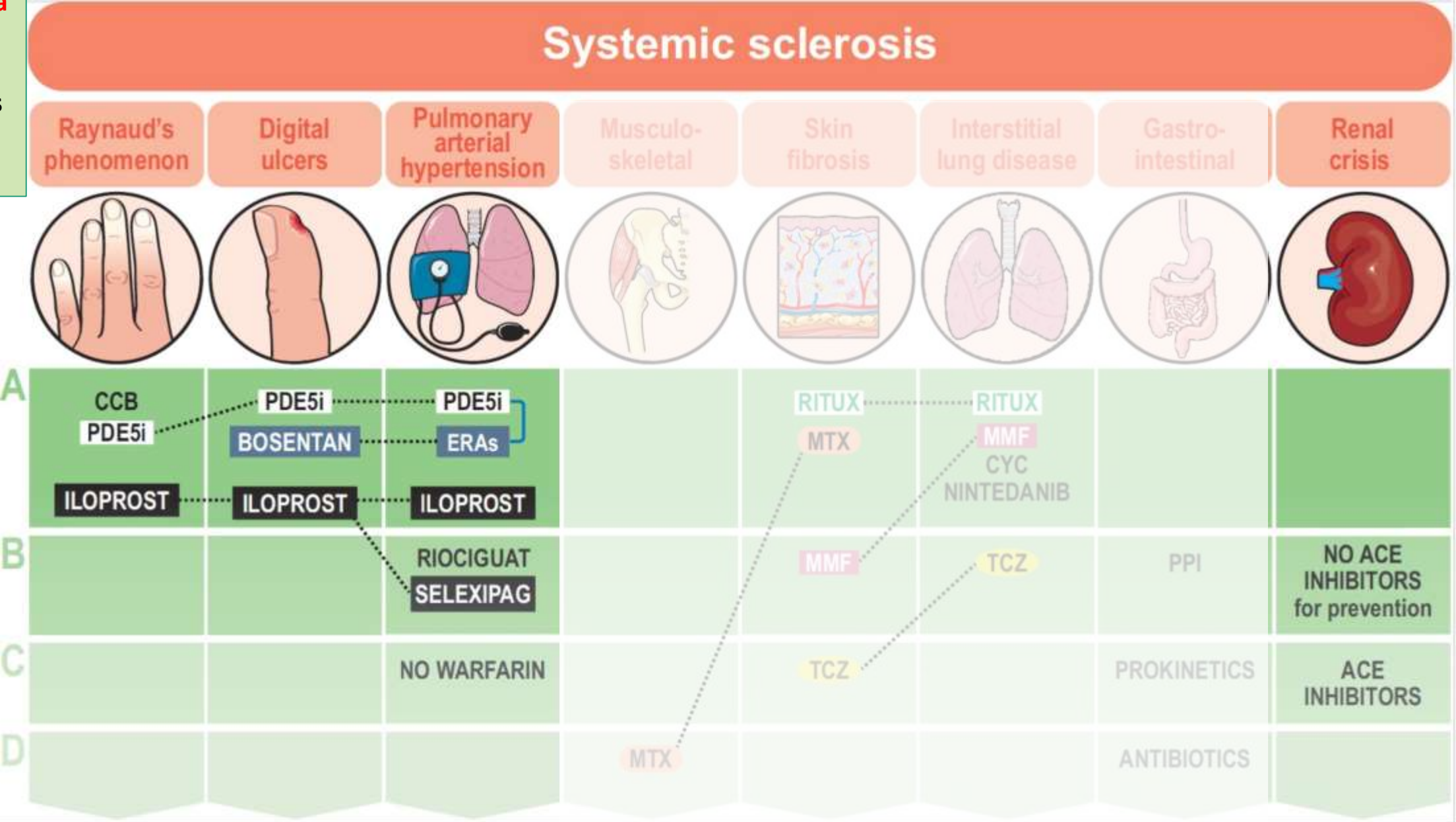
Kezelés:

Vascularis terápia

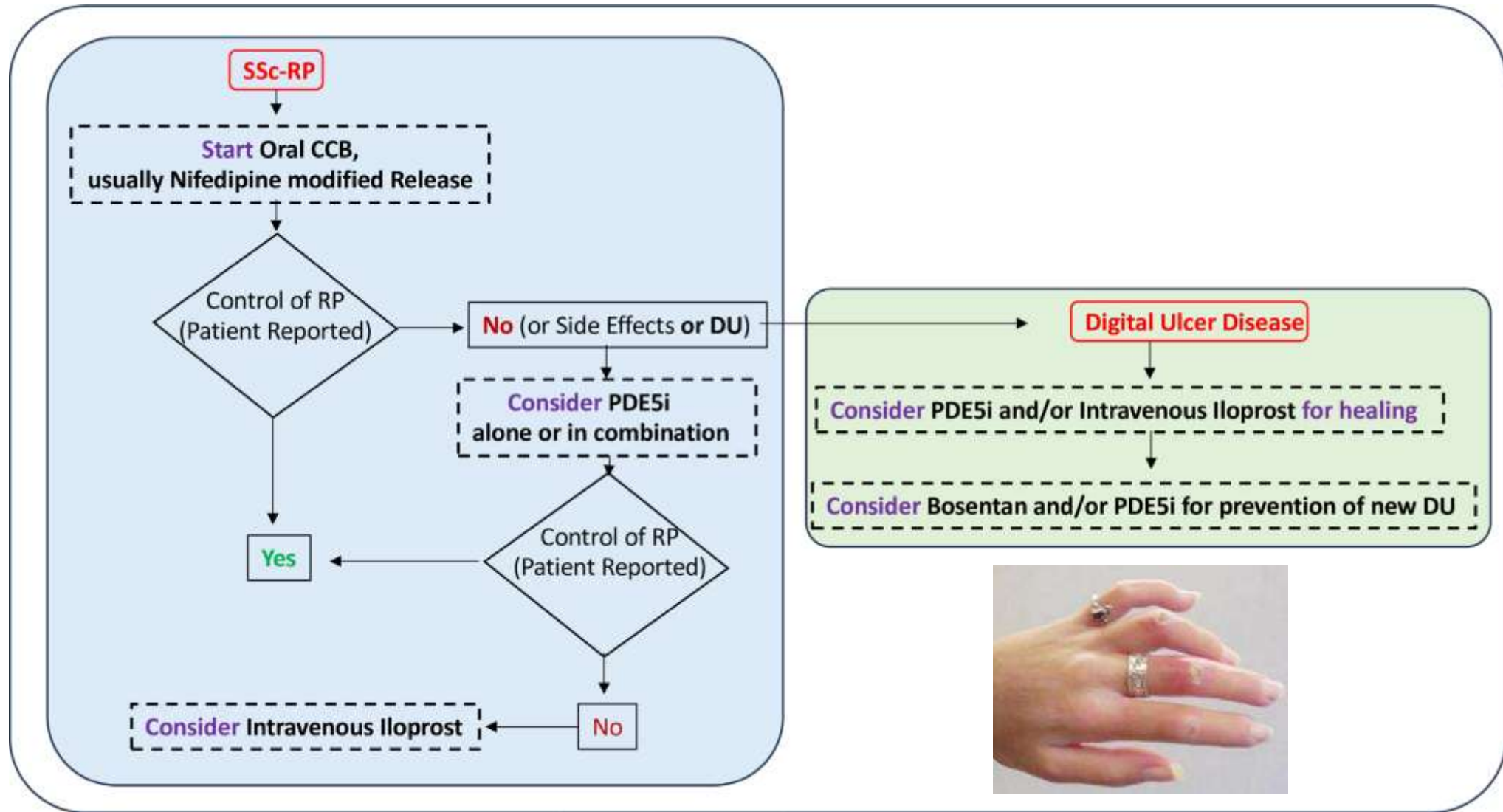
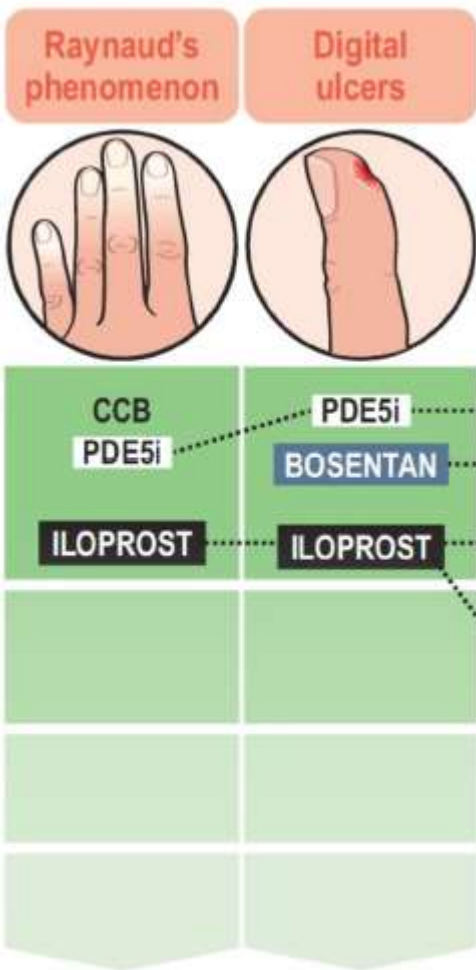
Immunszuppr./
Immunmoduláns

Antifibrotikus

SSc terápiás ajánlás – EULAR 2023

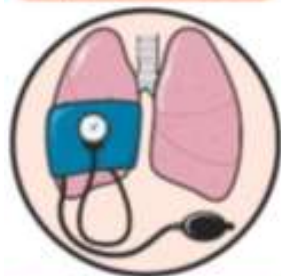


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SSc terapiás ajánlás – EULAR 2023

Pulmonary
arterial
hypertension



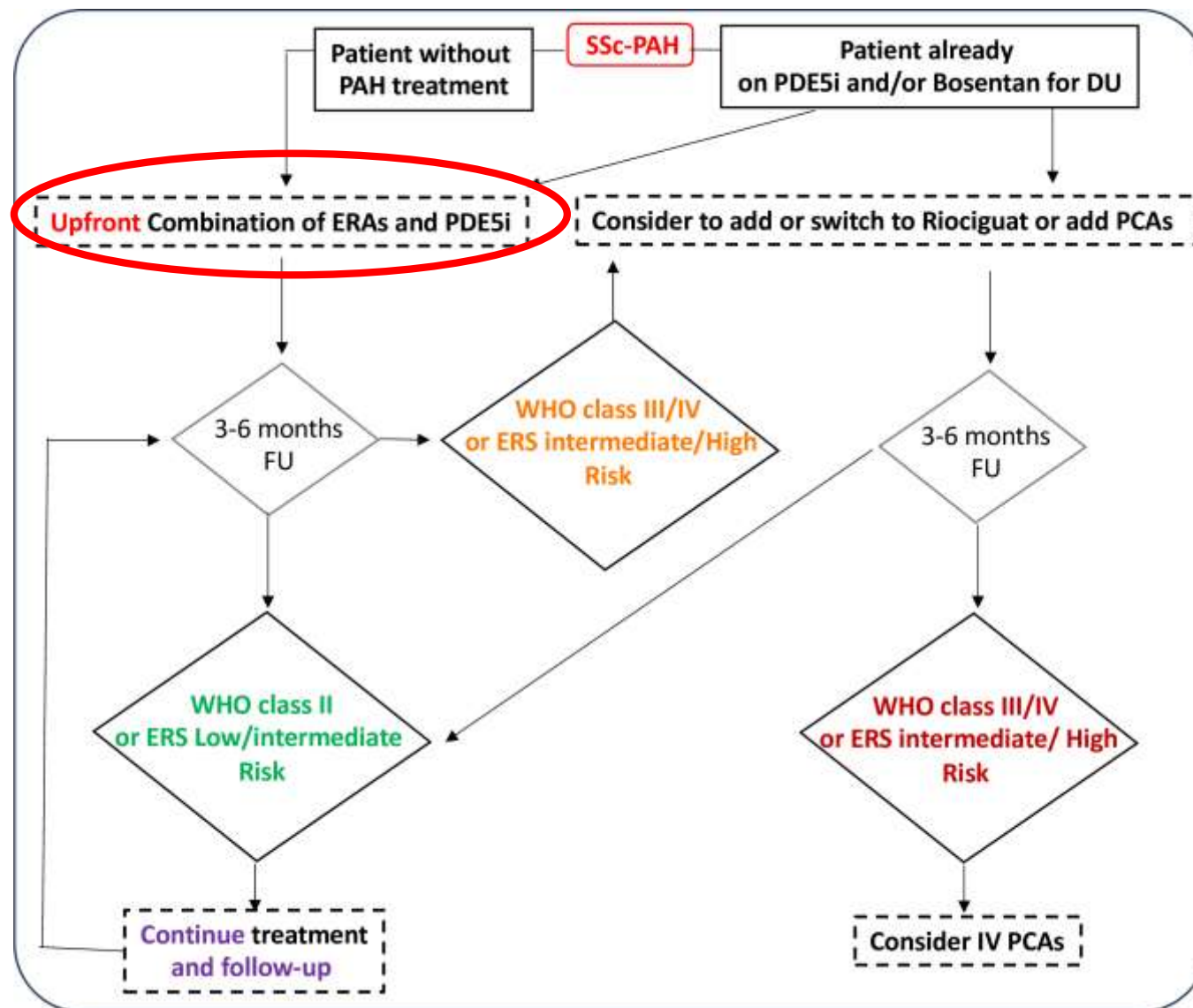
PDE5i
ERAs

ILOPROST

RIOCIGUAT
SELEXIPAG

NO WARFARIN

+
Iv epoprostenol



SSc – PAH kezelés

<https://emcrit.org/ibcc/pah/>

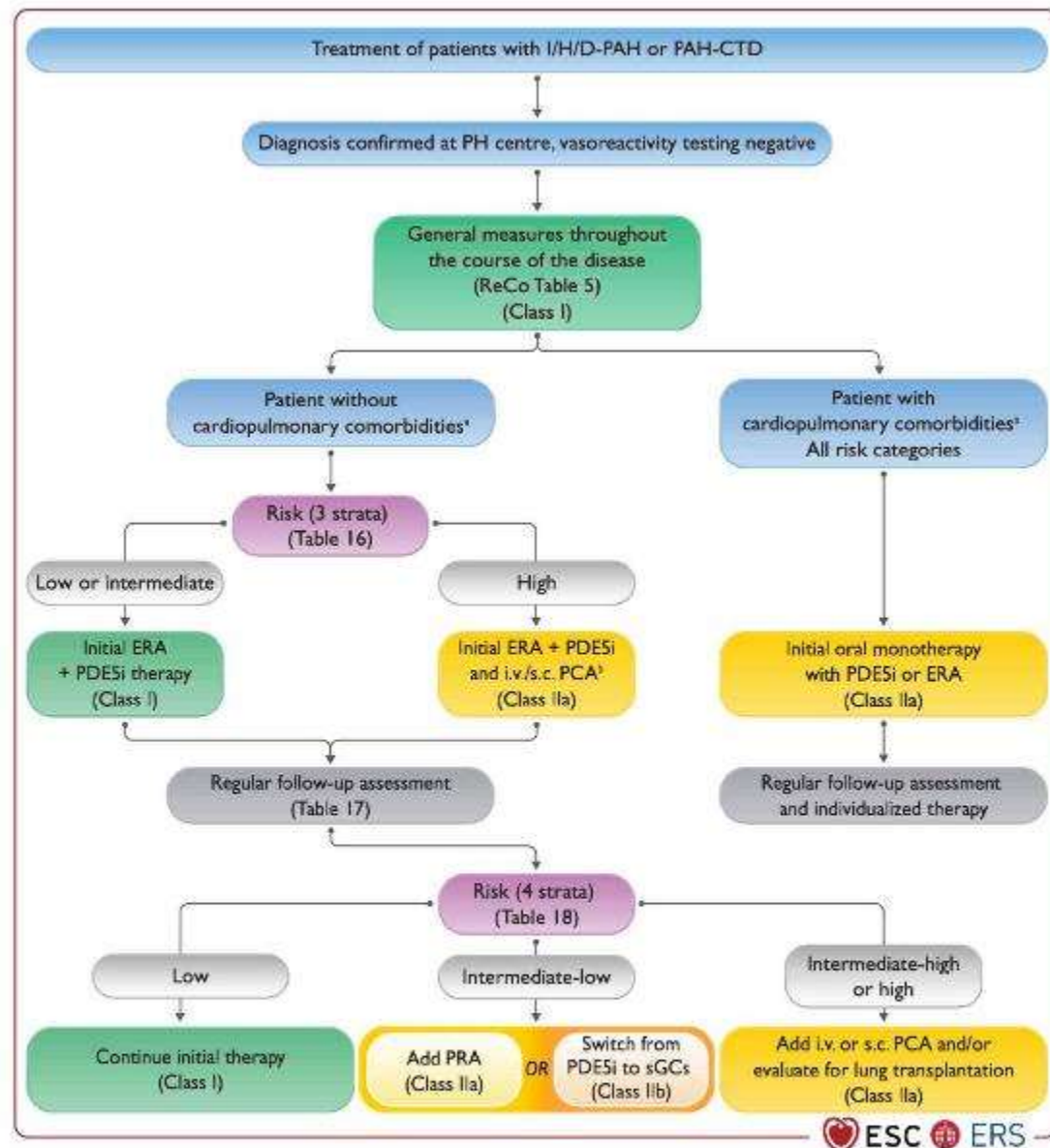


Figure 9 Evidence-based pulmonary arterial hypertension treatment algorithm for patients with idiopathic, heritable, drug-associated, and connective tissue disease-associated pulmonary arterial hypertension. DLCO, Lung diffusion capacity for carbon monoxide; ERA, endothelin receptor antagonist; I/H/D-PAH, idiopathic, heritable, or drug-associated pulmonary arterial hypertension; i.v., intravenous; PAH-CTD, PAH associated with connective tissue disease; PCA, prostacyclin analogue; PDE5i, phosphodiesterase 5 inhibitor; PH, pulmonary hypertension; PRA, prostacyclin receptor agonist; ReCo, recommendation; s.c., subcutaneous; sGCs, soluble guanylate cyclase stimulator. ^aCardiopulmonary comorbidities are conditions associated with an increased risk of left ventricular diastolic dysfunction, and include obesity, hypertension, diabetes mellitus, and coronary heart disease; pulmonary comorbidities may include signs of mild parenchymal lung disease and are often associated with a low DLCO (<45% of the predicted value). ^bIntravenous epoprostenol or i.v./s.c. treprostinil.

ISRCs	Expert consensus
Hypertensive SRC Any one of the following - a.) Systolic BP >140 mmHg or - b.) Diastolic BP >90 mmHg or - c.) Rise in systolic BP >30 mmHg compared to baseline or - d.) Rise in diastolic BP >20 mmHg compared to baseline AND One of the following features: - a.) Increase in sCr >50% over baseline or sCr >120% ULN for local laboratory - b.) Proteinuria >2+ on dipstick and confirmed by uPCR > ULN - c.) Hematuria: >2+ by dipstick or > 10 RBC/HPF (without mensuration) - d.) Thrombocytopenia <100 G/L - e.) Hemolysis on blood smear or increased reticulocyte count - f.) Hypertensive encephalopathy	A. Hypertensive SRC (fullfills both A1 and A2) 1. New onset hypertension, defined as any oft he following: - a.) Systolic BP $\geq$ 140 mmHg - b.) Diastolic BP $\geq$ 90 mmHg - c.) Rise in systolic BP $\geq$ 30 mmHg - d.) Rise in diastolic BP $\geq$ 20 mmHg AND 1. One (1) oft he following five (5) features - a.) Increase in sCr by >50% over baseline OR sCr $\geq$ 120% of ULN for local laboratory - b.) Proteinuria $\geq$2+ by dipstick - c.) Hematuria $\geq$2+ by dipstick or $\geq$ 10 RBC/HPF - d.) Thrombocytopenia <100 G/L - e.) Hemolysis defined as anemia not due to other causes and either of the following - i.) Schistocytes or other RBC fragments on blood smear - ii.) Increased reticulocyte count
Normotensive SRC Increase in sCr >50% over baseline or sCr >120% of ULN for local laboratory AND One of the following features: - a.) Proteinuria >2+ on dipstick and confirmed by uPCR > ULN - b.) Hematuria: >2+ by dipstick or > 10 RBC/HPF (without mensuration) - c.) Thrombocytopenia <100 G/L - d.) Hemolysis on blood smear or increased reticulocyte count - e.) Hypertensive encephalopathy	B. Normotensive SRC (fullfills both B1 and B2) 1. Increase in sCr $\geq$ 50% over baseline OR sCr $\geq$ 120% ULN for local laboratory AND 2. One (1) of the following five (5) features: - a.) Proteinuria $\geq$2+ by dipstick - b.) Hematuria $\geq$2+ by dipstick or $\geq$ 10 RBC/HPF - c.) Thrombocytopenia <100 G/L - d.) Hemolysis defined as anemia not due to other causes and either of the following - i.) Schistocytes or other RBC fragments on blood smear - ii.) Increased reticulocyte count - e.) Renal biopsy findings consistent with scleroderma renal crisis (microangiopathy)

Renalis manifesztáció

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+ egyéb antitenzív terápia

ET-1Ra – nem hatékony

PEX:? – SSc+MAHA

eculizumab

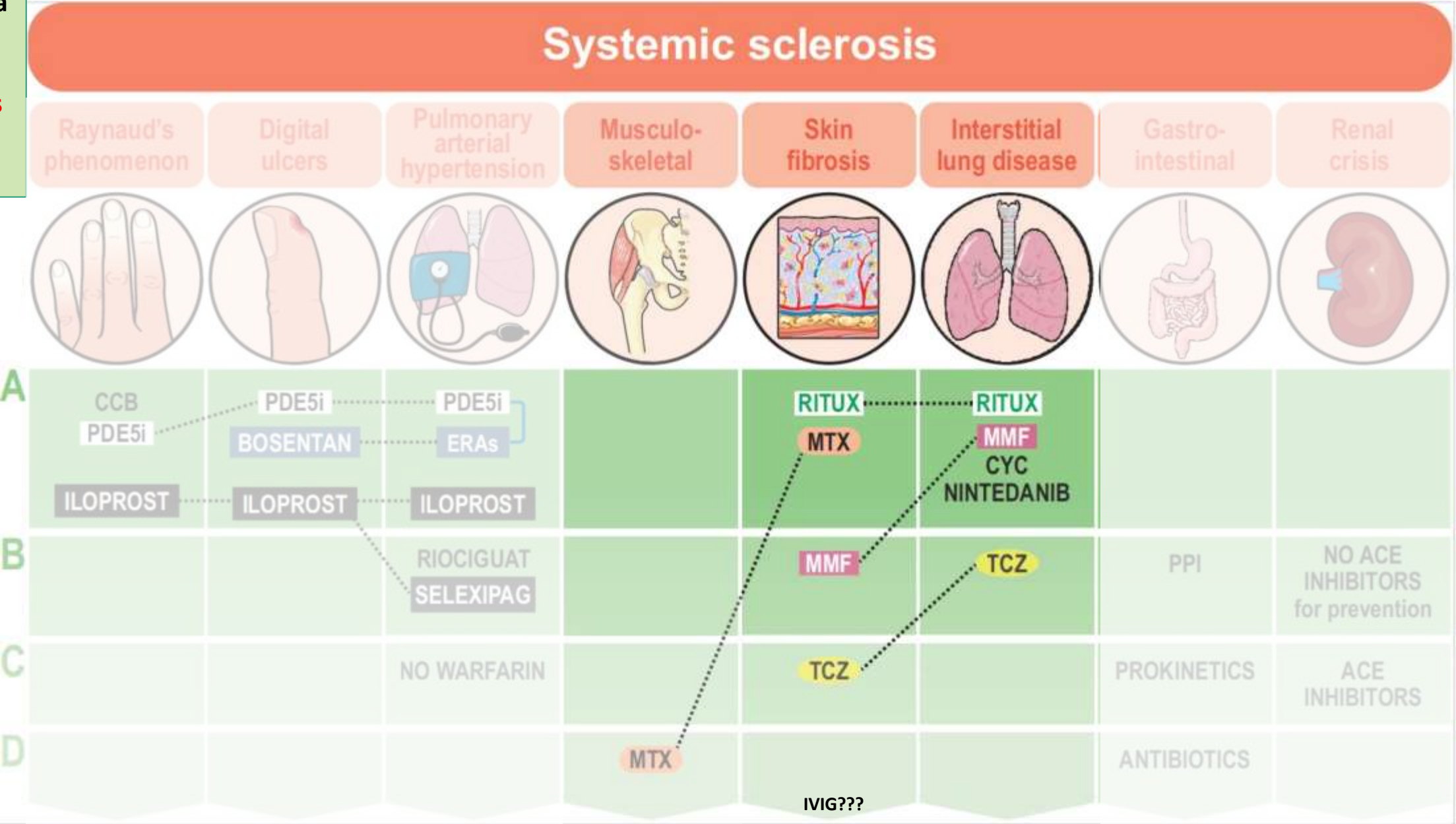
Kezelés:

Vascularis terápia

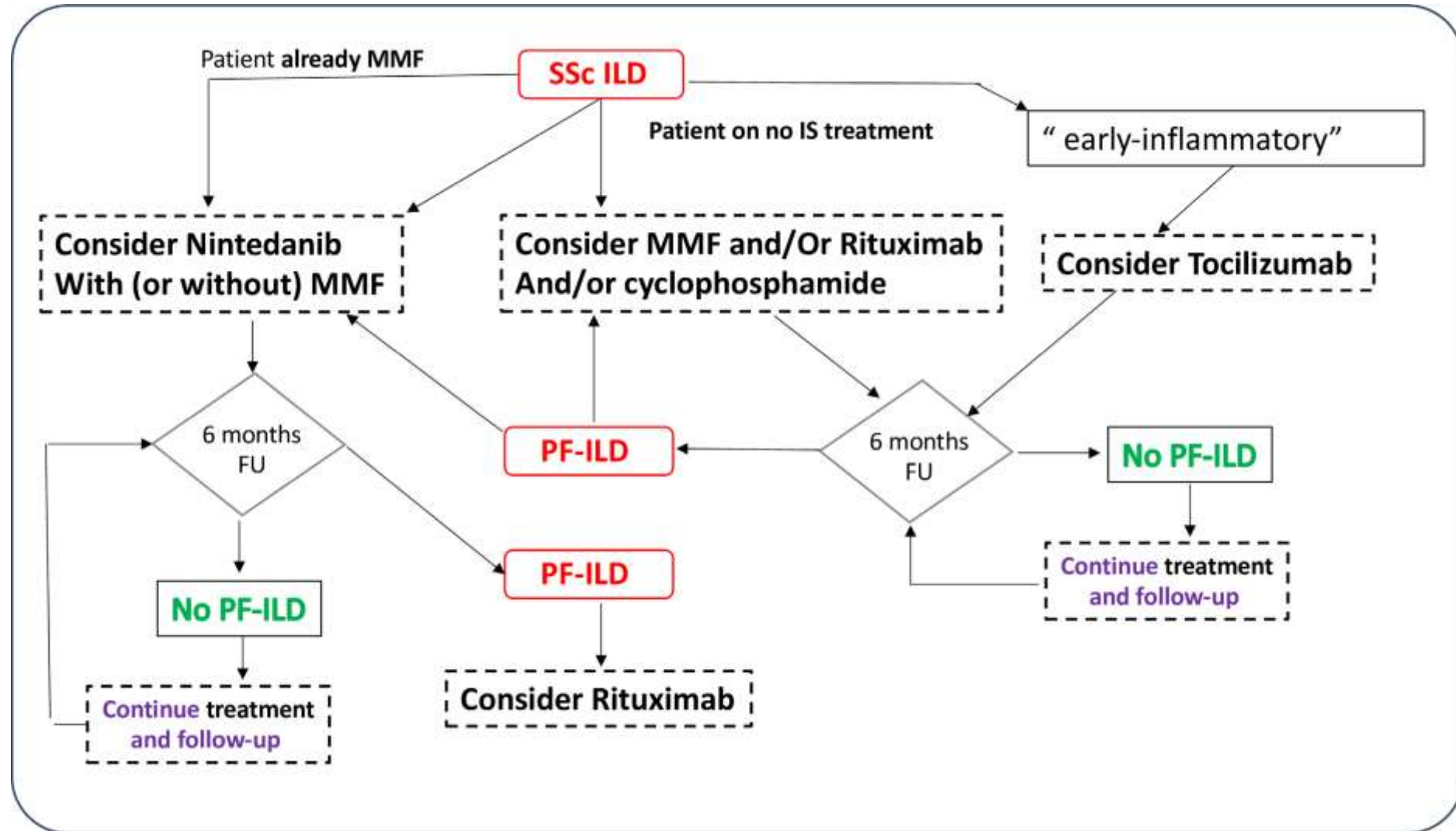
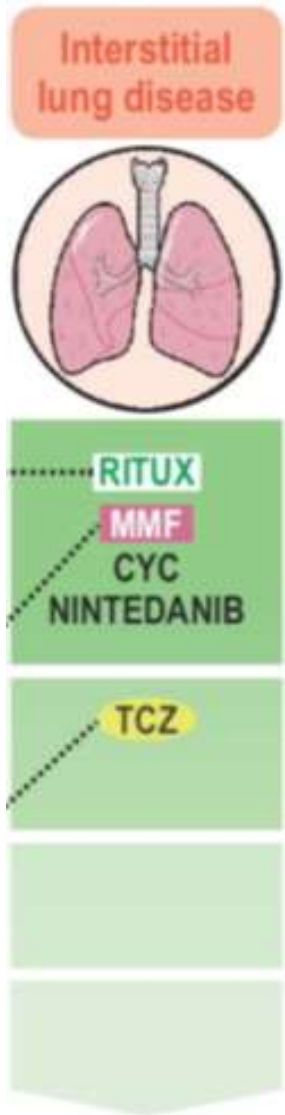
Immunszuppr./
Immunmoduláns

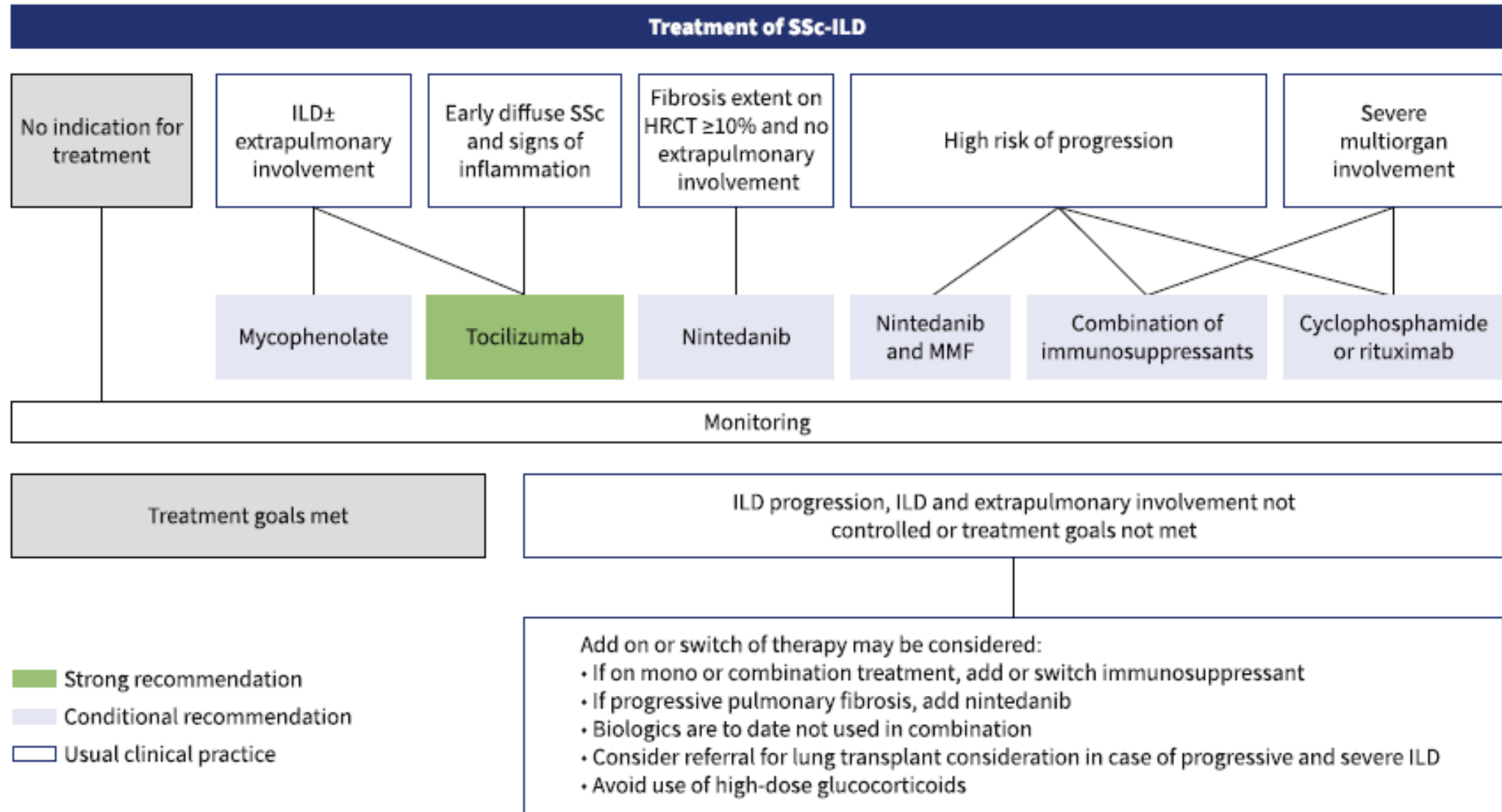
Antifibrotikus

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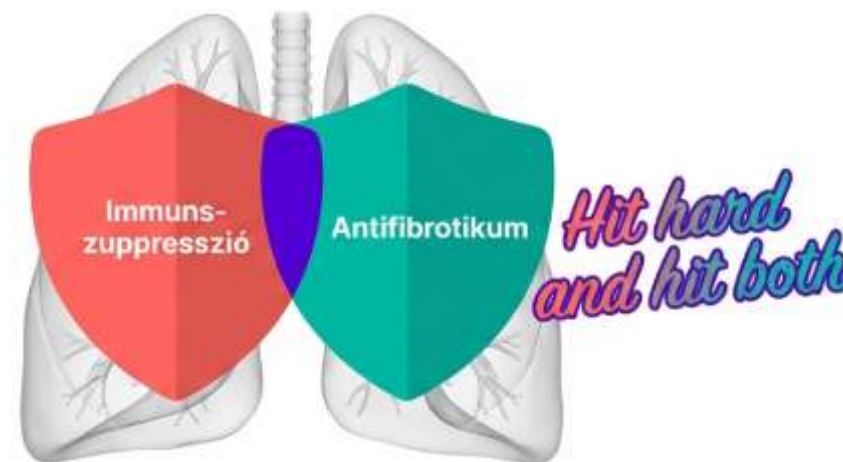
Kombinációs kezelések

Kevés RCT adat:

- RTX + MMF > mono MMF
- MMF + NTD > NTD

RWE:

- TCZ + MMF > mono TCZ
- Hármas kombináció NTD+TCZ+MMF
- IIM-ILD: MMF+RTX+NTD ($\pm$ GC)
- RA-ILD: csDMARD+bDMARD+NTD/Pirfenidon

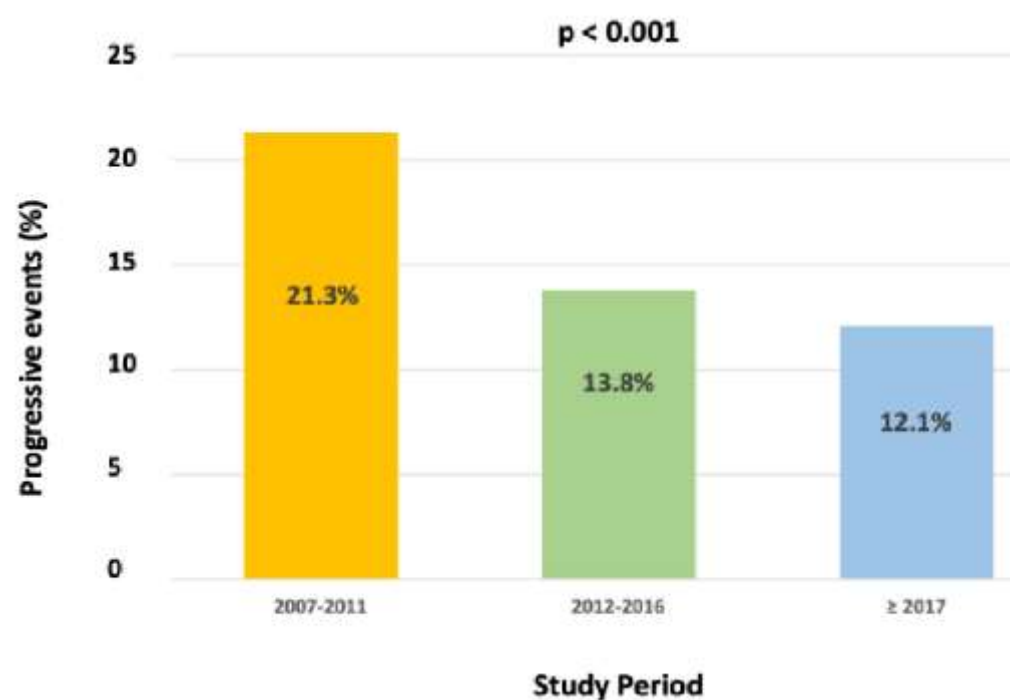


INFEKCIÓ RIZIKÓ!

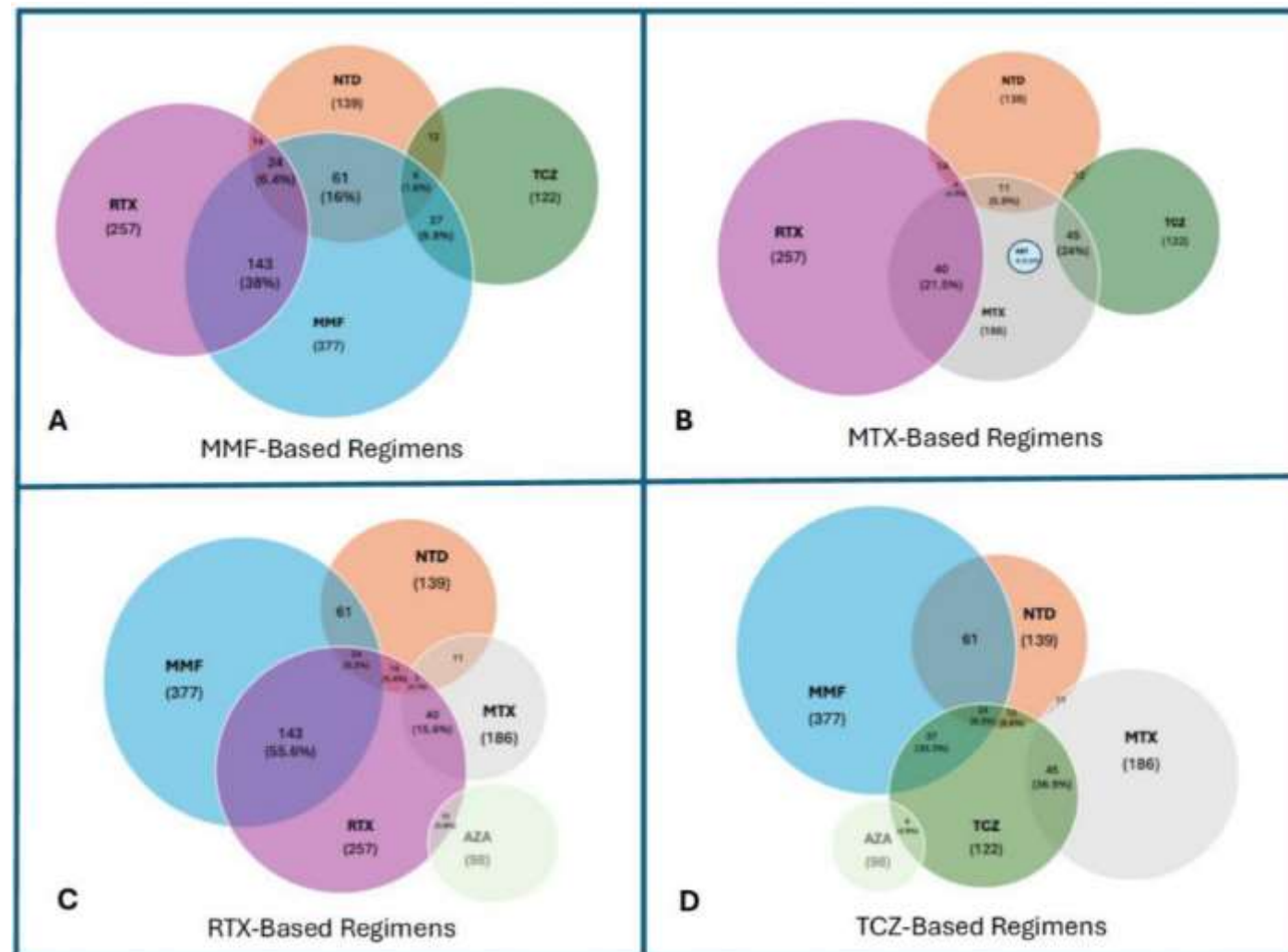
VAKCINÁCIÓ!

SSc-ILD – EUSTAR adatok

1409 SSc-ILD beteg



≥2017

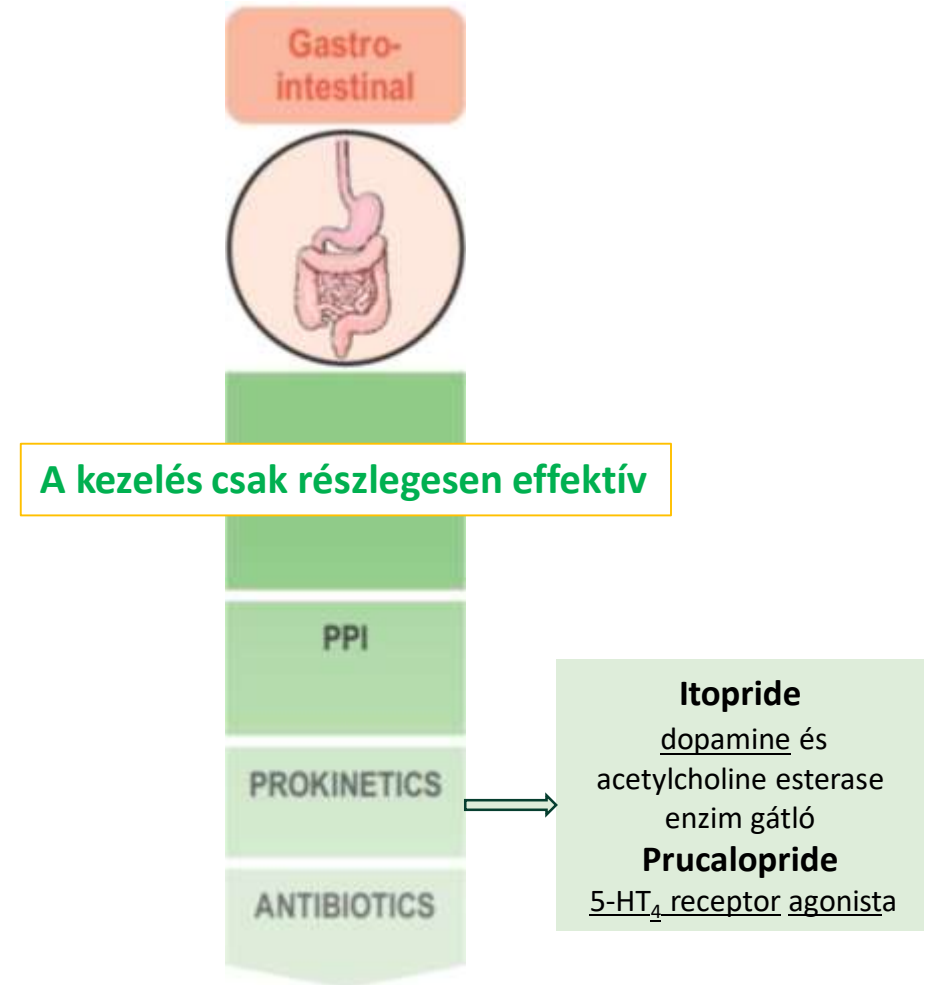
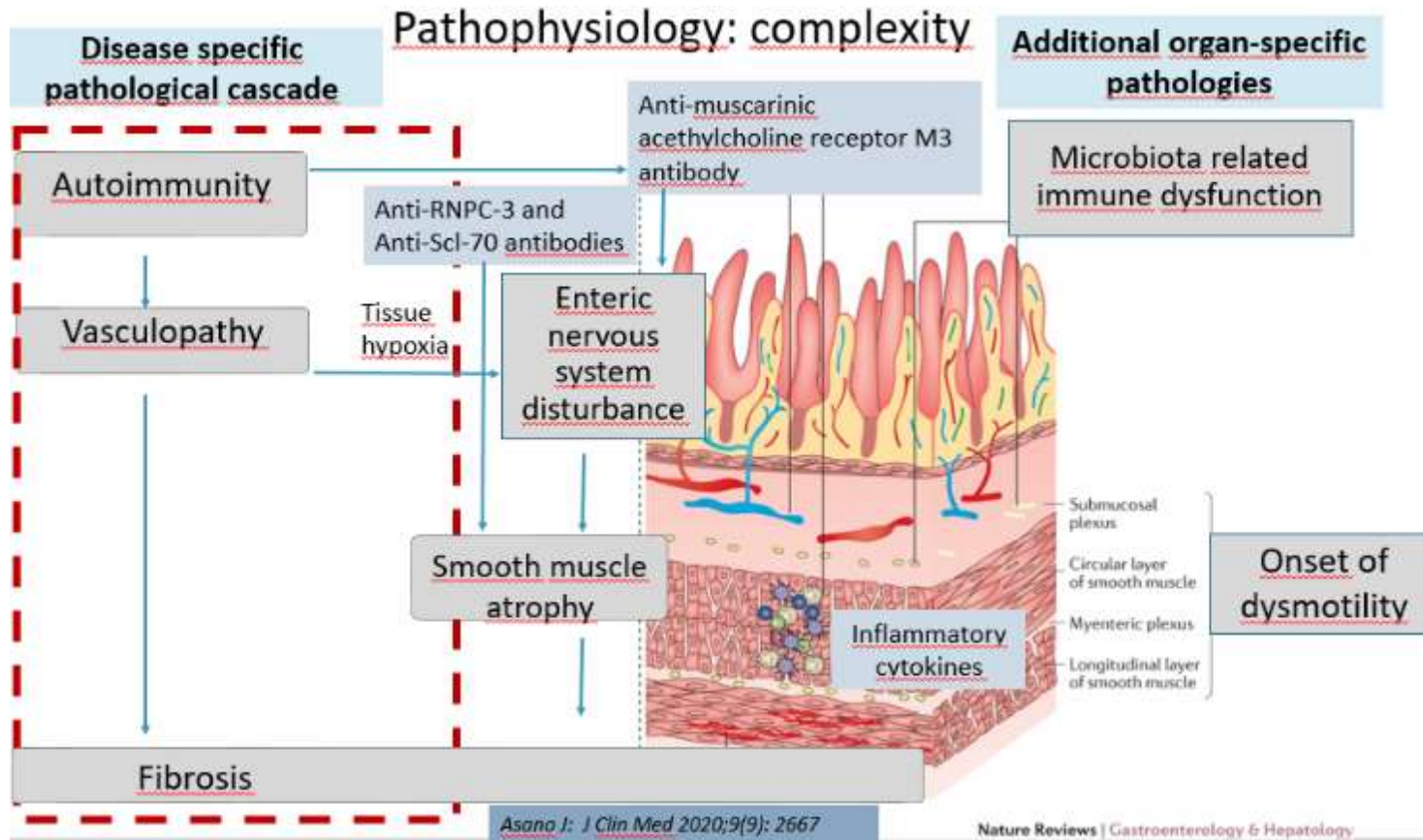


SSc terapiás ajánlás – EULAR 2023

Systemic sclerosis							
Raynaud's phenomenon	Digital ulcers	Pulmonary arterial hypertension	Musculo-skeletal	Skin fibrosis	Interstitial lung disease	Gastro-intestinal	Renal crisis
A CCB	PDE5i	PDE5i		RITUX MTX	RITUX MMF CYC NINTEDANIB		
Nagy intenzitású ISU kezelés – HSCT Korai, rossz prognózisú beteg							
B		RIOCIGUAT SELEXIPAG		MMF	TCZ	PPI	NO ACE INHIBITORS for prevention
C		NO WARFARIN		TCZ		PROKINETICS	ACE INHIBITORS
D			MTX			ANTIBIOTICS	

Gasztrointesztinális manifesztációk

SSc terápiás ajánlás – EULAR 2023



IVIG? Autoimmun Rev 2023; 22(11): 103441.

209 SSc beteg ISU kezeléssel: alacsonyabb GIT score a követés során RMD Open 2024;10:e004333. doi:10.1136/rmdopen-2024-004333

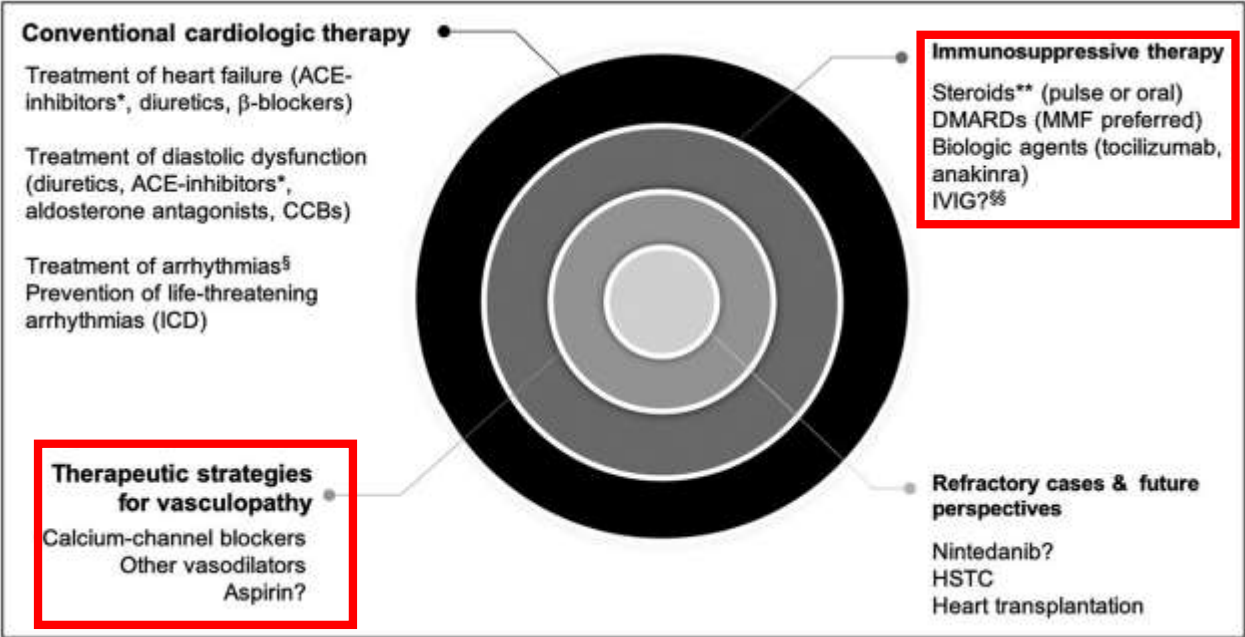
Savcsökkentő kezelés: csökkenti a MMF biohasznosulását Semin Arthritis Rheum 2023; 63: 152270.

Heart involvement in patients with systemic sclerosis—what have we learned about it in the last 5 years

Table 2 Current treatment options among systemic sclerosis patients with heart involvement depending on the clinical manifestation

Type of heart involvement	Treatment options
Myocarditis	DMARDs (such as: AZA, MMF, MTX, CYC) alone or with GCs [82, 83] Symptomatic treatment
Pericarditis	NSAIDs (carefully) Colchicine GCs [49]
Arrhythmia	Similar to the general population [12, 16, 82] B-blocker (carefully; cardioselective) Ivabradine (sinus tachycardia > 70/min) Oral anticoagulation, Pacemaker, ICD—if necessary [49, 82]
HFpEF	Diuretics for fluid retention Dapagliflozin/ Empagliflozin Treatment for an etiology, CV and non-CV comorbidities [49, 53, 84]
HFmrEF	Diuretics for fluid retention Dapagliflozin/ Empagliflozin ACEI/ ARNI/ ARB, MRA, B-blocker (carefully; cardioselective)—may be considered [49, 53, 84]
HFrEF	ACEI (carefully in SRC high risk patients)/ ARNI B-blocker (carefully; cardioselective) MRA Dapagliflozin/ Empagliflozin Loop diuretics for fluid retention CRT, ICD (in selected cases) [49, 53, 84]

+anti-IL6, anti-IL1, RTX?



20 SSc-ILD – nintedanib: beneficial effects of nintedanib on SSc-pHI
(Rheumatology (Oxford) 2022; 62:2550–2555.)

SSc calcinosis

Hydroxyapatite és amorf calcium phosphate kristályok

Szignifikáns morbiditás, életminőség csökkenés

Prevalencia 18-49% (lcSSc ~ dcSSc
ACA, anti-PM/Scl + - magasabb prevalencia

Progresszió gyakoribb: ffi beteg, DU,
osteoporosis, ILD

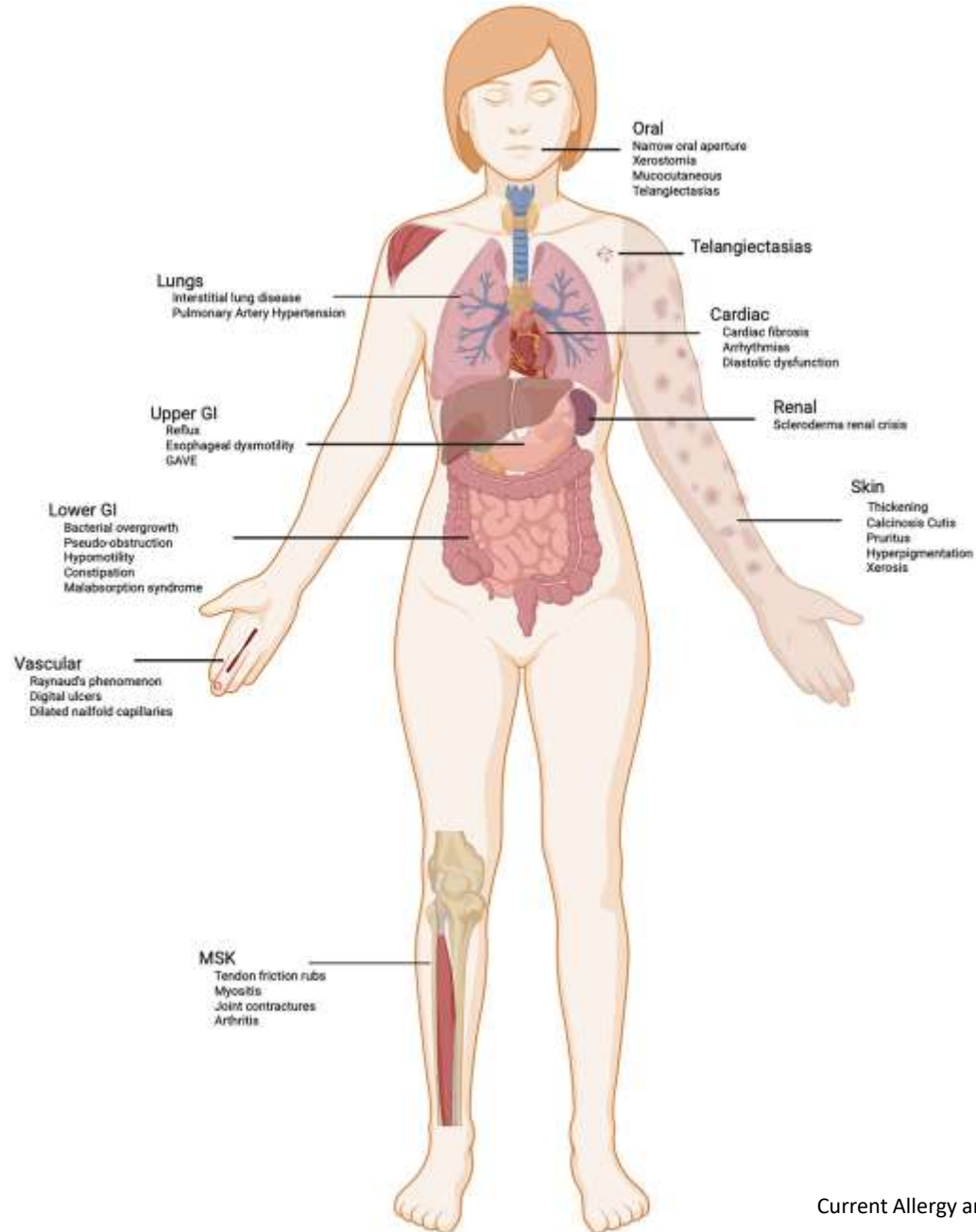
Nincs hatékony kezelés!



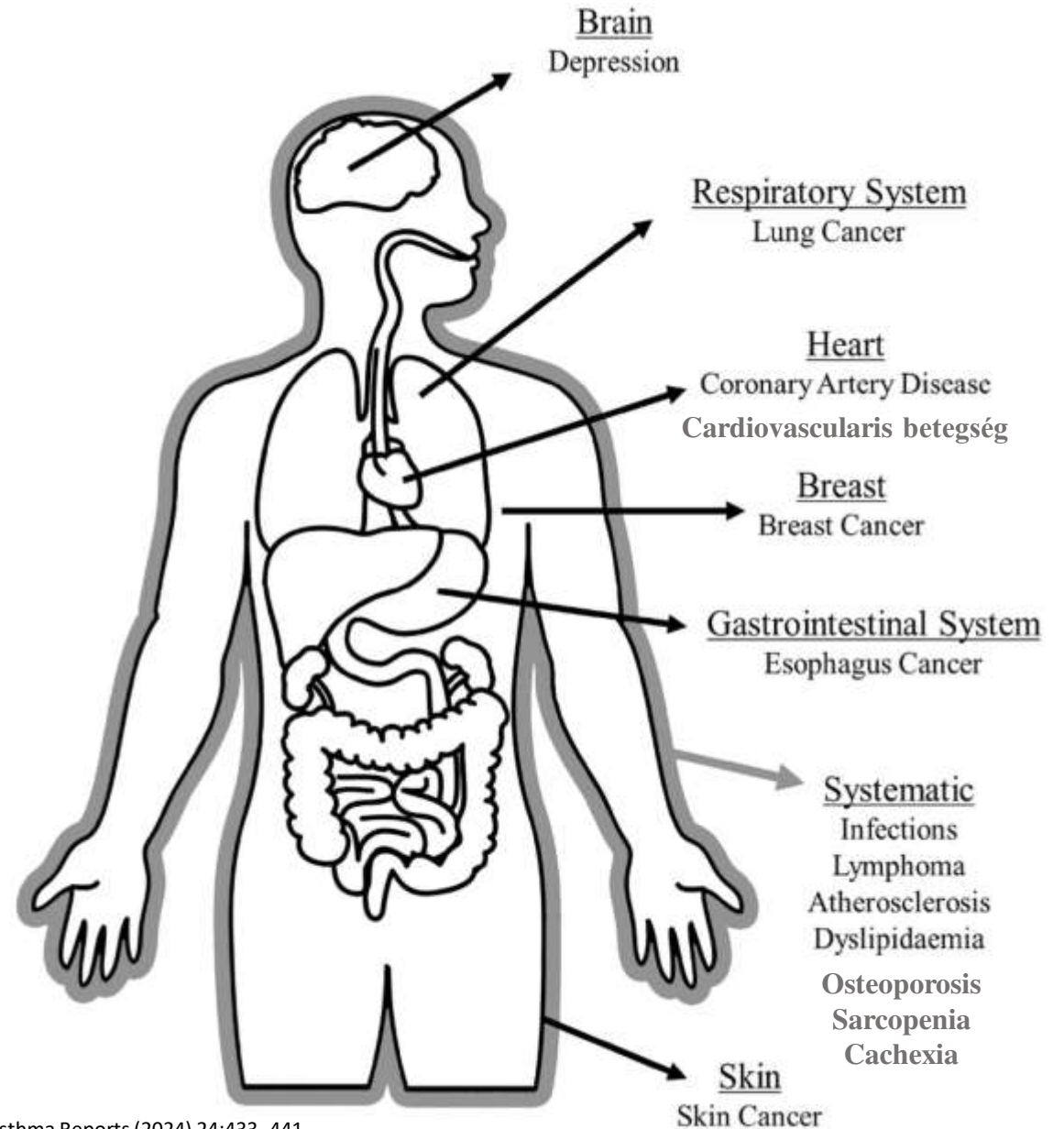
Table 2. Summary of theories for the pathophysiology of calcinosis cutis.

Mechanism	Evidence
Chronic inflammation	Increased production of TNF, IL-1, IL-6, and other proinflammatory cytokines
Vascular hypoxia (ischemia)	Hypoxia-induced imbalance between angiogenic factors (such as VEGF, platelet-derived growth factors) and antiangiogenic factors (such as angiostatin, endostatin) Increased expression of the hypoxia-associated GLUT-1 Hypoxia-induced osteoclast activity
Recurrent trauma	Presence or history of digital ulcers Calcification occurs at sites of chronic trauma/stress, suggesting a role of pressure or recurrent trauma

A SSc szervi manifesztációi



SSc komorbiditások



SSc komorbiditások – napi gyakorlat

Dg. felállításakor: malignitás szűrése – RNSPIII+!

Követés során rendszeres szűrés

Cardiovascularis szűrések: rendszeresen

anamnézis - fizikális vizsgálat – eszközös vizsgálatok (EKG, card UH stb.)

Osteoporosis – szűrés (DEXA) – D-vitamin pótlás!!!

Egyéb társbetegségek – BMI, sarcopenia, depresszió stb.

Antifibrotikus kezelés

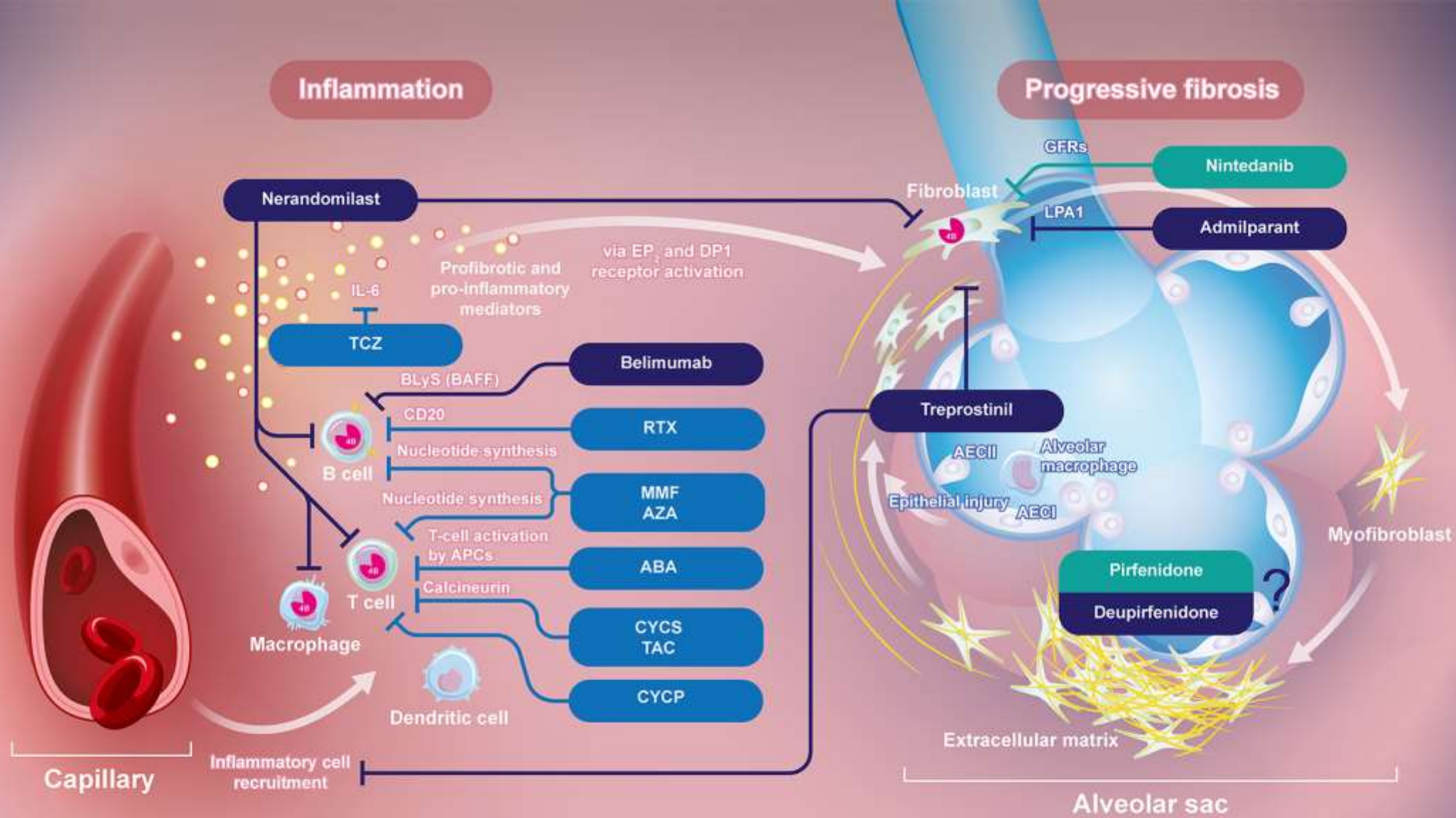
Standard of care

Current Paradigm

Nintedanib (Tyrosine kinase inhibitor) & Pirfenidone (TGF-β modulator)

Emerging terápiák

Mechanism	Drug	Indication	Phase	Key endpoint
PDE4 inhibitor	Nerandomilast	IPF/PPF	Approved (2025/2026)	FVC change
LPA1 antagonist	Admilparant	IPF/PPF	Phase 3 (ALOFT)	FVC change
Integrin antagonist	Bexotegrast	IPF	Phase 2b/3 (BEACON-IPF)	FVC and biomarkers
Prostacyclin analogue	Treprostinil (inhalative)	IPF/PPF	Phase 3 (TETON)	FVC change
Autotaxin inhibitor	BBT-877	IPF	Phase 2	FVC change
Hedgehog inhibitor	Taladegib	IPF/PPF	Phase 2b (WHISTLE-PF)	Safety/FVC
AT2R agonist	Buloxibutid	IPF	Phase 2b (ASPIRE)	FVC change

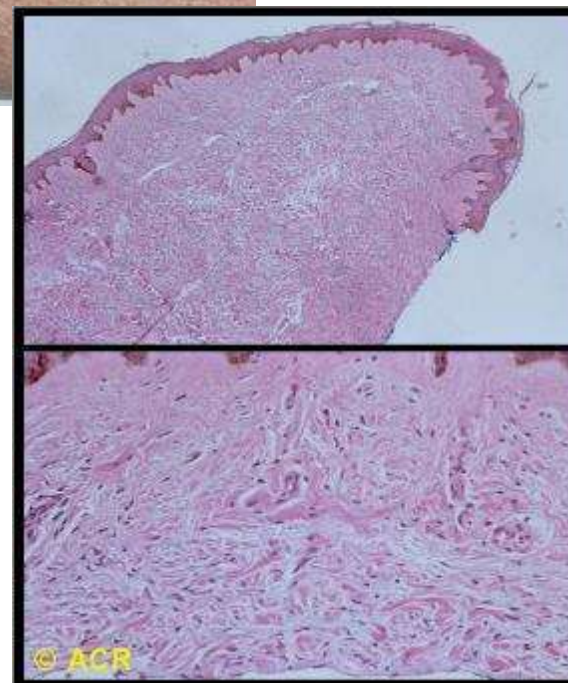


Morgan ND et al. Curr Treatm Opt Rheumatol. 2016 March ; 2(1): 69–84.
doi:10.1007/s40674-016-0038-7.

LOCALIZED		
<u>Morphea</u>		
Linear Generalized Pansclerotic		
SYSTEMIC		
<u>Inflammatory & Immune mediated</u>	<u>Hereditary</u>	
★ Eosinophilic fasciitis Graft versus host disease Lichen sclerosus et atrophicus POEMS syndrome *	Congenital fascial dystrophy Progeroid disorders - Progeria - Acrogeria - Werner's syndrome	
<u>Deposition Disorders</u>	<u>Metabolic</u>	
★ Scleromyxedema Systemic amyloidosis ★ Nephrogenic systemic fibrosis ★ Scleredema adultorum Lipodermatosclerosis	Hypothyroidism (myxedema) Phenylketonuria Porphyria cutanea tarda	
<u>Occupational Exposure</u>	<u>Toxin & Chemical Induced</u>	
Epoxy resins Organic solvents Polyvinyl chloride Silica	Pharmaceuticals	Pesticides
	Balicatib Bisoprolol Bleomycin Bromocriptine Carbidopa D-Penicillamine L-tryptophan Pentazocine Postradiation fibrosis Toxic oil syndrome	Diniconazole Malathion
		Chemicals
		Benzene Malathion Naphthalene Toluene Trichloroethylene Vinyl chloride monomers

Scleromyxoedema

- 30-50 éves korban, férfi:nő = 1:1
- monoclonalis gammopathia (IgG lambda könnyű lánc)
- ritkán daganatos betegség/infectiohoz társul
- arc, törzs, végtagok bőre érintett
- belszervi tünetek potenciálisan súlyosak (oesophagus dysmotilitás, veseelégtelenség, izomgyengeség)
- Raynaud phenomen hiányzik
- Mucin depositumok az érfalban és a dermisben
 - Terápia:
 - prednisolon
 - melphalan
 - cyclophosamid
 - chloroquin
 - PUVA, fotopheresis
 - plasmapheresis
 - **IVIG**



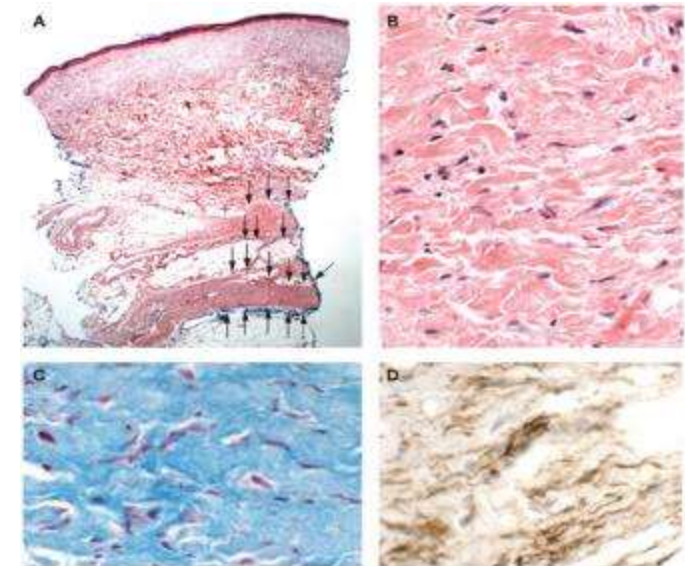
Scleredema adultorum Buschke

- **Diabetes mellitus**
 - Gyerekekben infectiohoz társul
 - monoclonalis gammopathia gyakori
 - Nyak, hát (ujjak nem)
 - Collagen ↑↑, kevés mucin lehet
-
- **Terápia:**
 - prednisolon
 - D-penicillamin
 - PUVA, fotopheresis



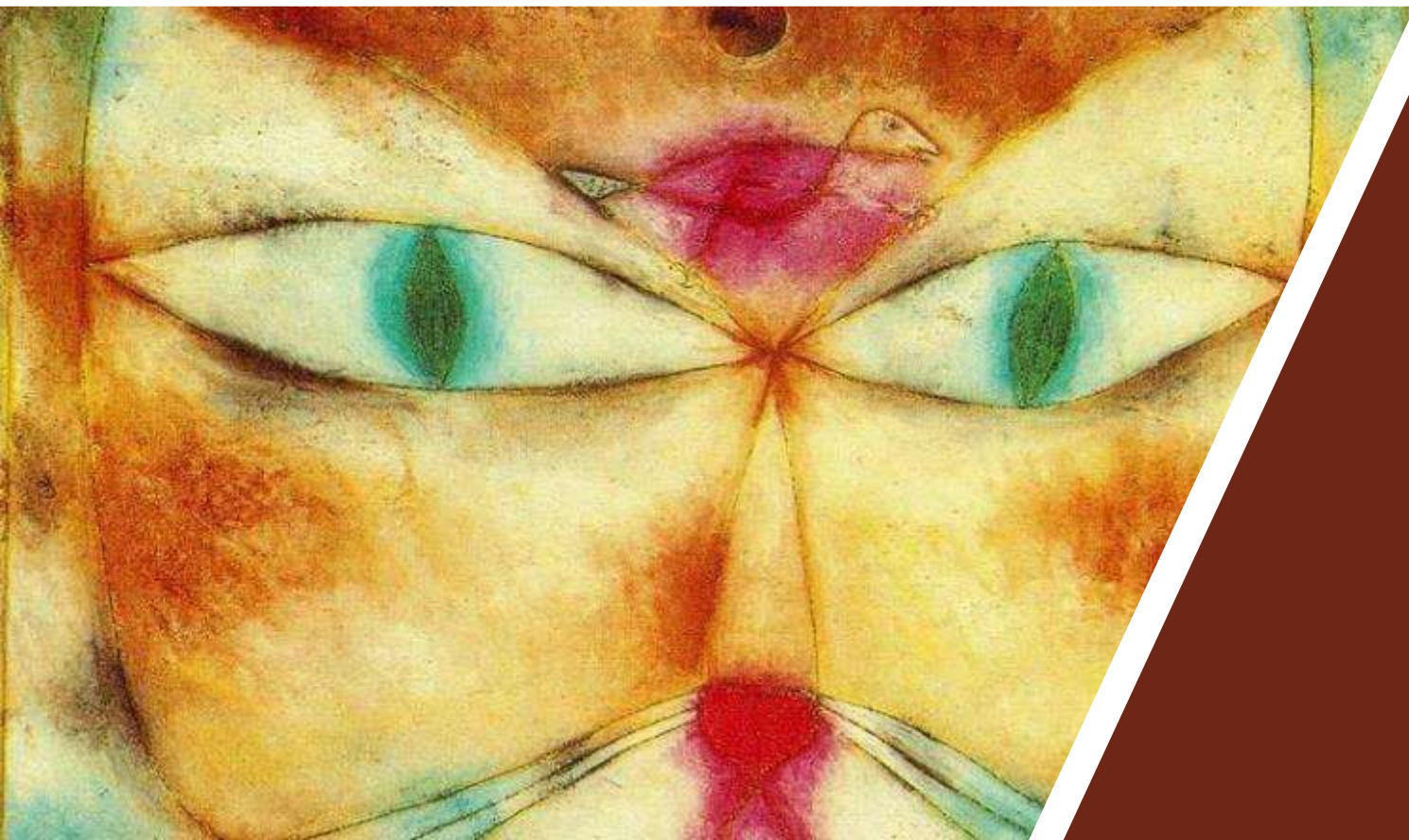
Nephrogen systemas fibrosis

- © 2000-ben írták le először dializált betegekben
- © a bőr megvastagodása, hyperpigmentáció, de az ujjak megkíméltek!) „narancsbőr” jellegű
- © belszervek fibrosisa: izom, myocardium, tüdő
- © trigger: nagy dózisú erythropoetin, **gadolinium tartalmú kontrasztanyag (MR angio!)**
- © dg alapja a szövettan: bőr teljes vastagságára kiterjedő fibrosis, csillag alakú és osteoclast-szerű óriássejtek





1879-1940



KÖSZÖNÖM A
FIGYELMET!