ILD 환자의 자가면역질환 동반여부 감별

: 류마티스내과적 접근

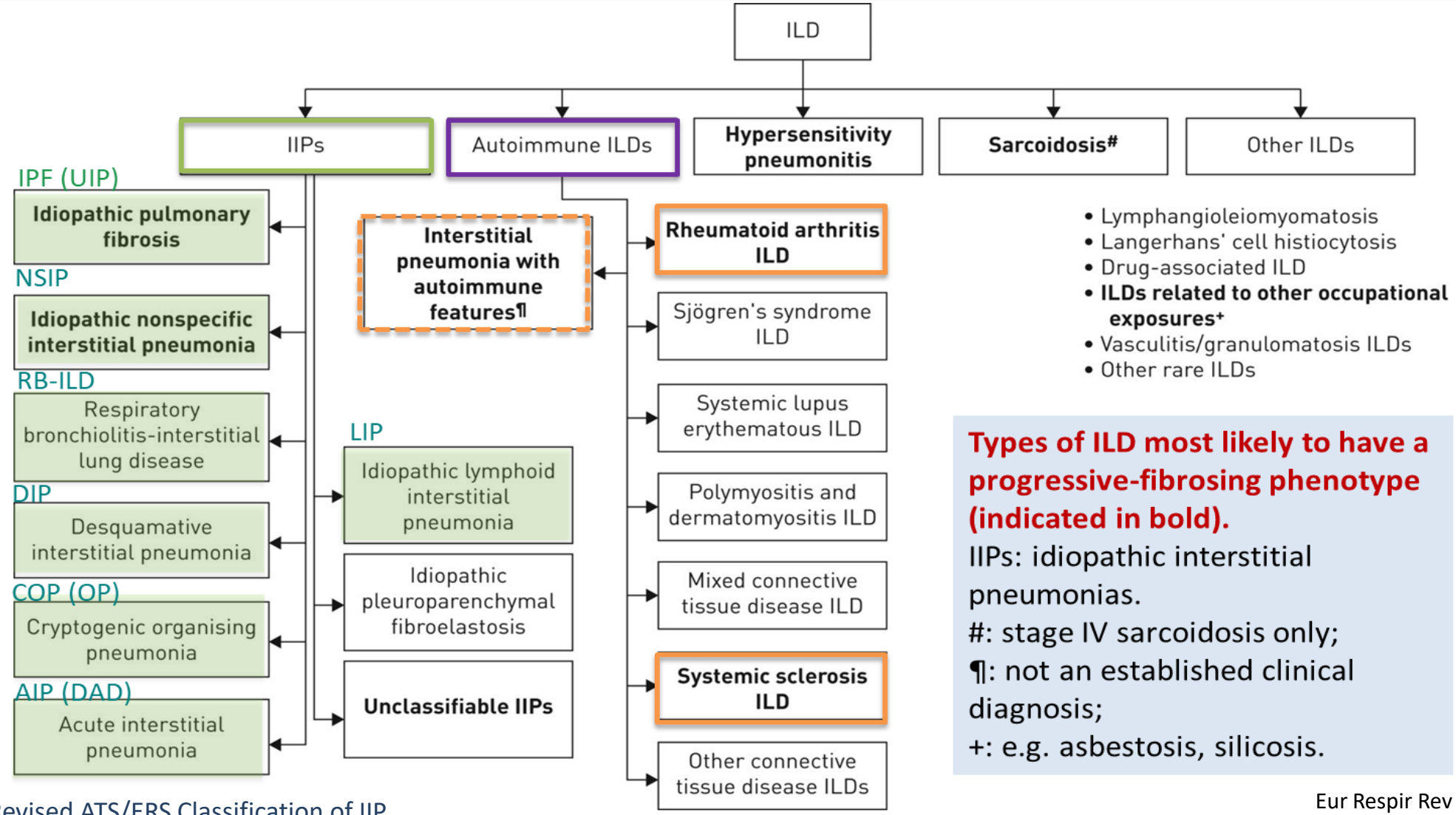
경희의대 류마티스내과
이연아

2023.06.24

Topics

- **CTD-ILD**
  - Classification
  - Pathogenesis
  - Prognostic factors
- **Diagnostic considerations**
  - Clinical clues suggestive of concomitant CTD
  - AutoAb, Biomarkers
  - Monitoring Algorithm
- **Therapeutic considerations**
  - MTX use, DMARDs
  - Biologics

Classification of ILD



Types of ILD most likely to have a progressive-fibrosing phenotype (indicated in bold).

IIPs: idiopathic interstitial pneumonias.

#: stage IV sarcoidosis only;

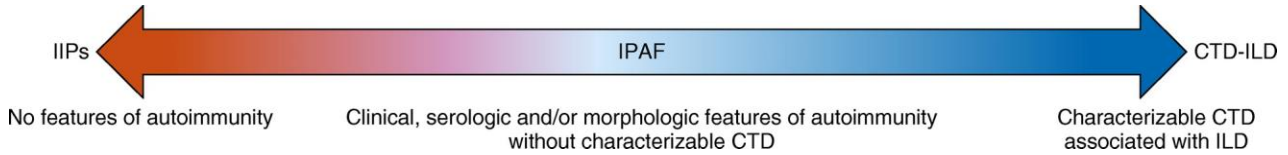
¶: not an established clinical diagnosis;

+: e.g. asbestosis, silicosis.

2013 Revised ATS/ERS Classification of IIP

Eur Respir Rev 2018; 27: 180076

Classification Criteria for IPAF



Ann Am Thorac Soc 2019; 16(5): 525–33

1. Presence of an interstitial pneumonia by HRCT or SLB *and*
2. Exclusion of alternative etiologies *and*
3. Does not meet criteria for a defined CTD *and*
4. At least one feature from at least two of the following domains:

CT에서 ILD소견 + 다른 원인 배제+ CTD 진단기준에는 못 미치는 경우이면서 임상적, 혈청학적, 형태학적 domain 중 2가지 이상 domain 에 해당하는 소견을 보이는 경우

A. Clinical domain

1. Distal digital fissuring (i.e., "mechanic hands")
2. Distal digital tip ulceration
3. Inflammatory arthritis *or* polyarticular morning joint stiffness ⩾60 min
4. Palmar telangiectasia
5. Raynaud phenomenon
6. Unexplained digital edema
7. Unexplained fixed rash on the digital extensor surfaces (Gottron sign)

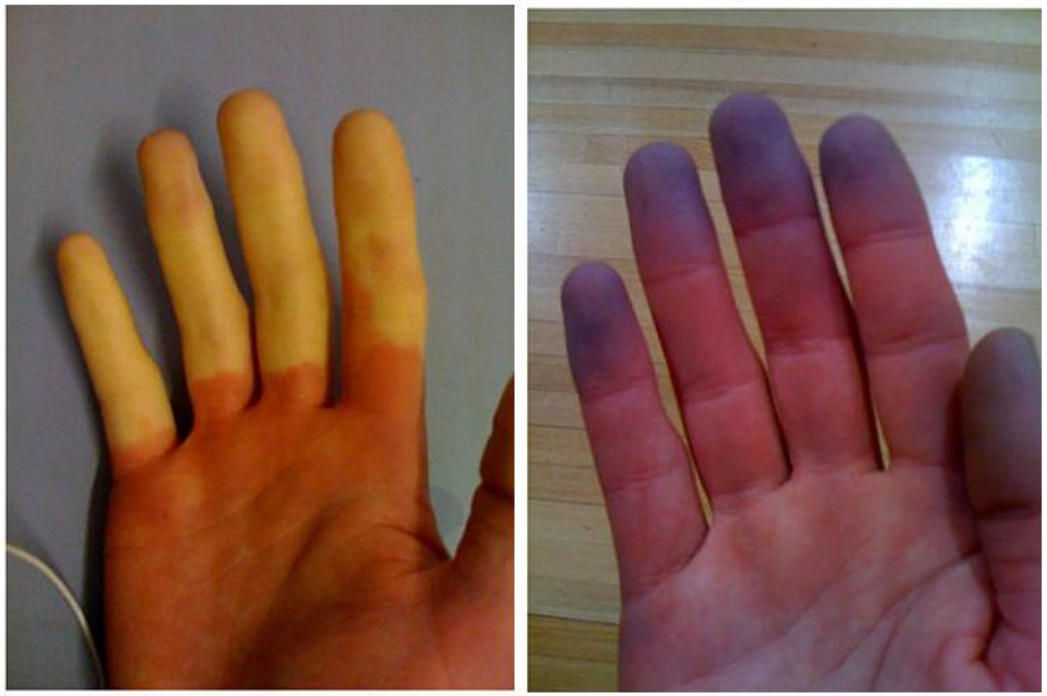
B. Serologic domain

1. ANA ⩾ 1:320 titer, diffuse, speckled, homogeneous patterns *or*
   a. ANA nucleolar pattern (any titer) *or*
   b. ANA centromere pattern (any titer)
2. Rheumatoid factor ⩾2 × upper limit of normal
3. Anti-CCP
4. Anti-dsDNA
5. Anti-Ro (SS-A)
6. Anti-La (SS-B)
7. Anti-ribonucleoprotein
8. Anti-Smith
9. Anti-topoisomerase (Scl-70)
10. Anti-tRNA synthetase (e.g., Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, tRS)
11. Anti–PM-Scl
12. Anti–MDA-5

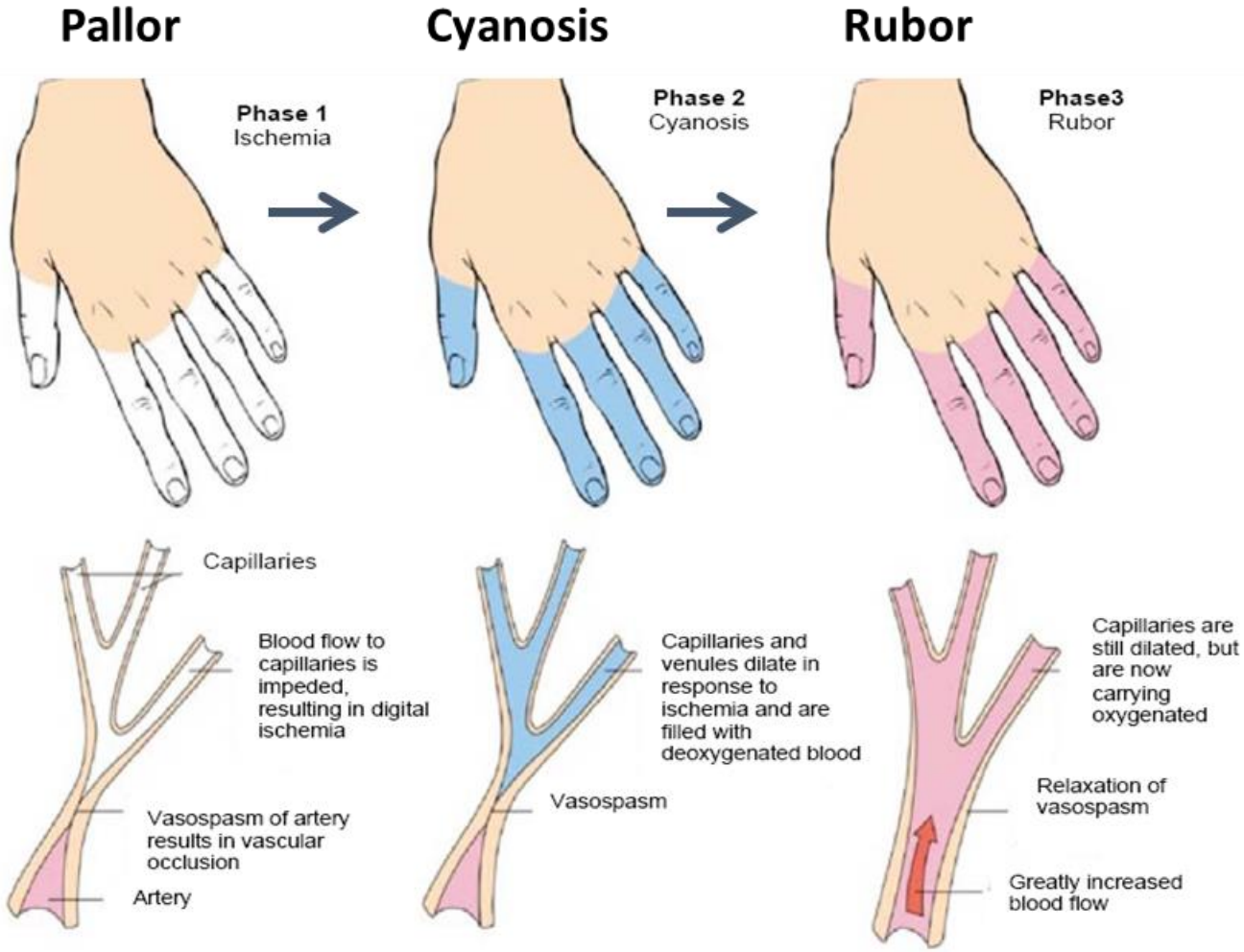
C. Morphologic domain

1. Suggestive radiology patterns by HRCT:
   a. NSIP
   b. OP
   c. NSIP with OP overlap
   d. LIP
2. Histopathology patterns or features by surgical lung biopsy:
   a. NSIP
   b. OP
   c. NSIP with OP overlap
   d. LIP
   e. Interstitial lymphoid aggregates with germinal centers
   f. Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)
3. Multicompartment involvement (in addition to interstitial pneumonia):
   a. Unexplained pleural effusion or thickening
   b. Unexplained pericardial effusion or thickening
   c. Unexplained intrinsic airways disease* (by PFT, imaging or pathology)
   d. Unexplained pulmonary vasculopathy

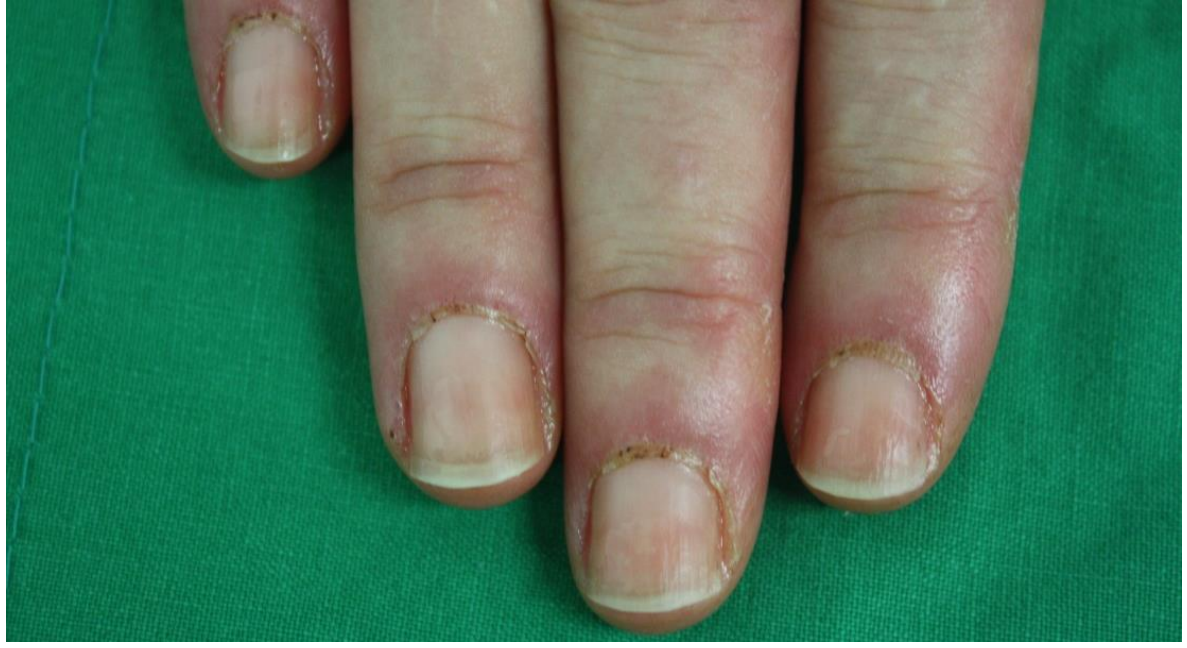
Raynaud's Phenomenon (RP)



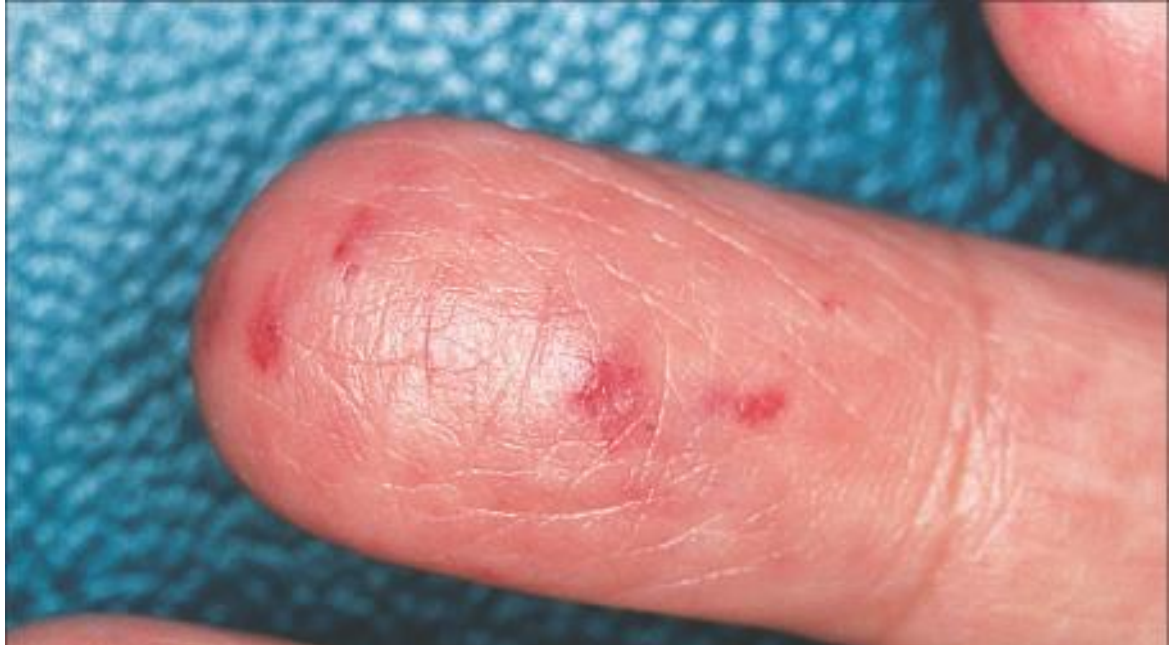
경계가 분명한 색조변화-diagnostic hallmark



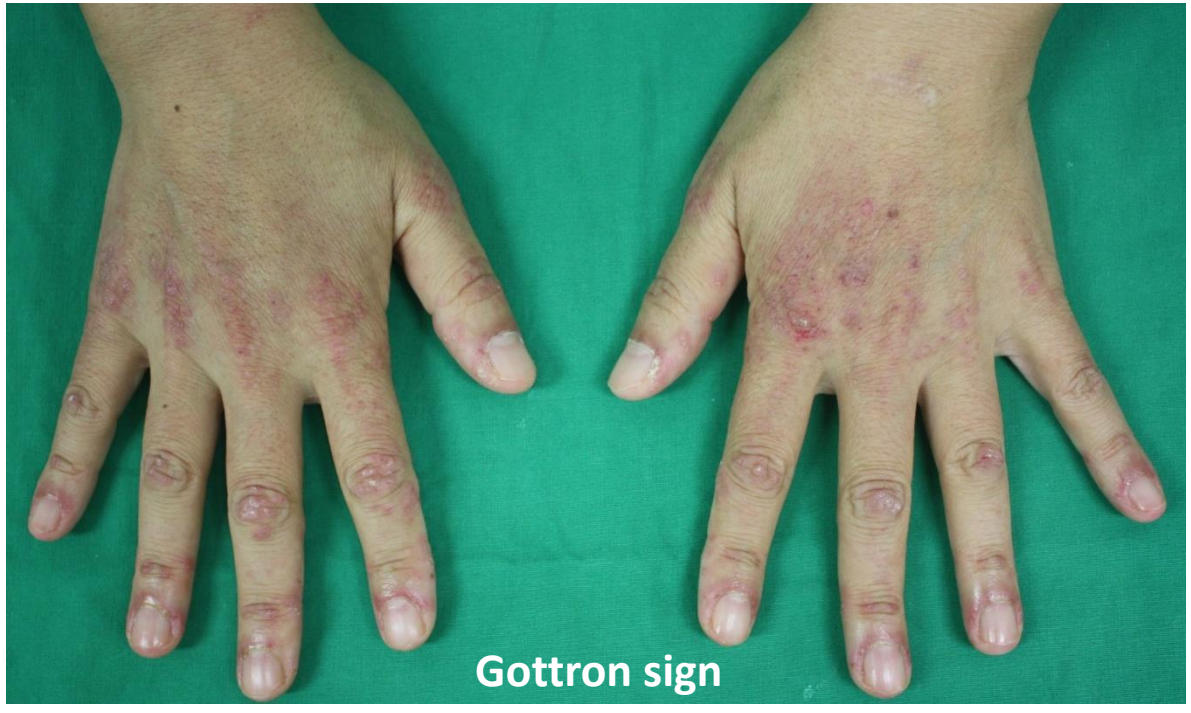
전형적으로 3단계 , 때로 2단계 (창백, 청색)

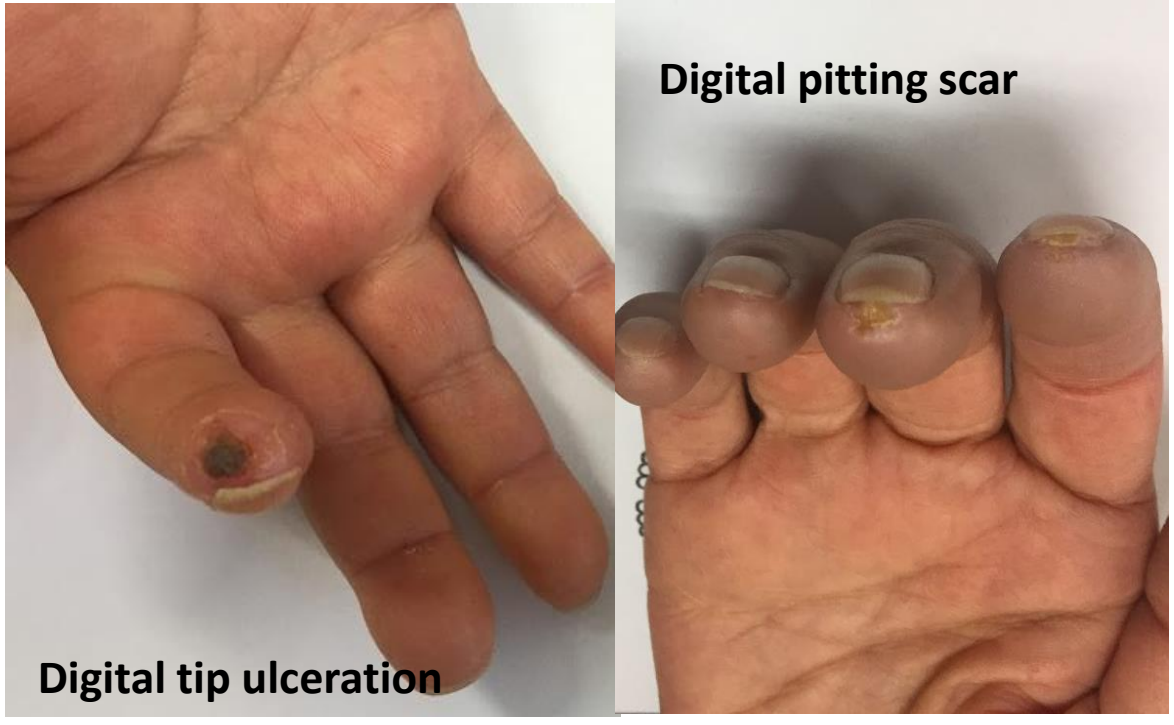


Mechanic’s hand

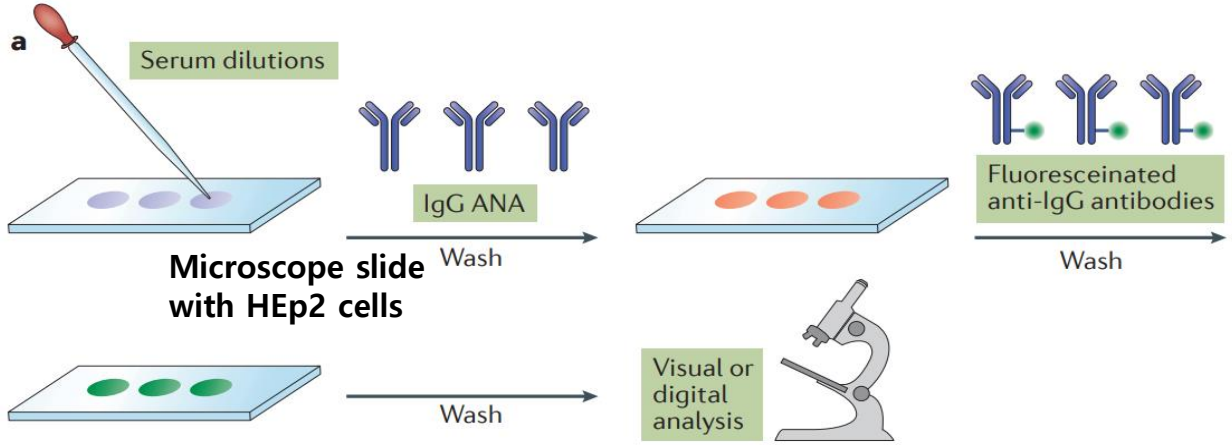


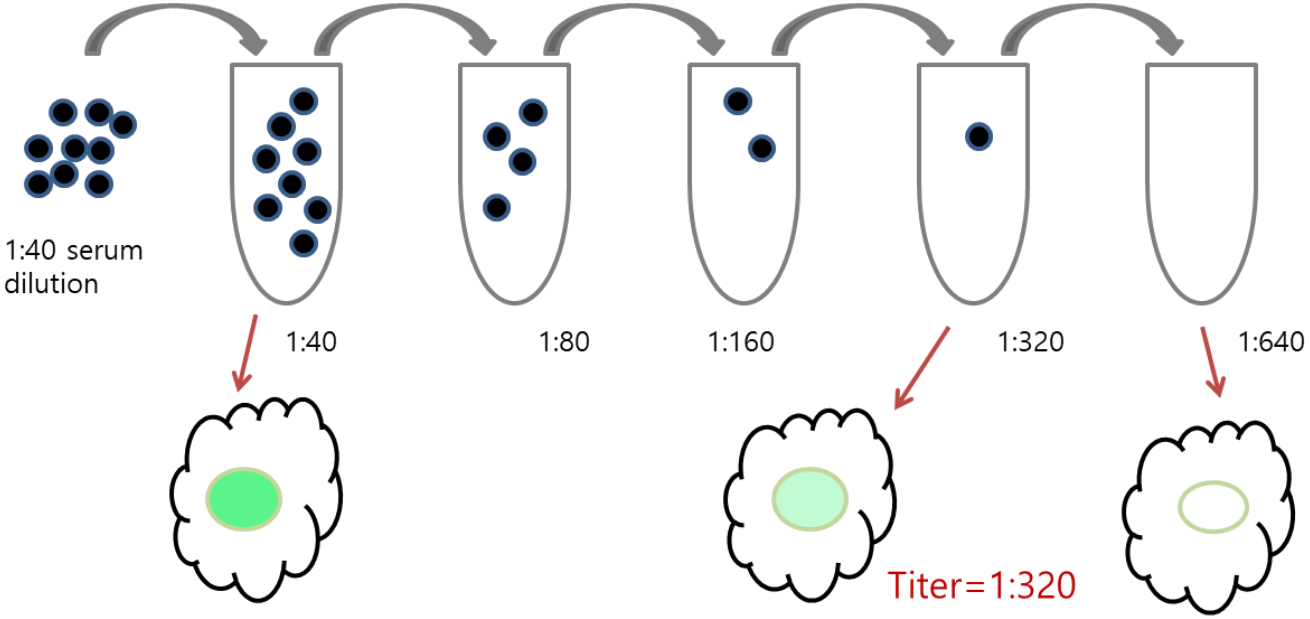
Telangiectasia

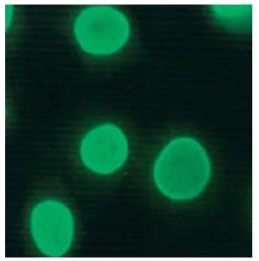


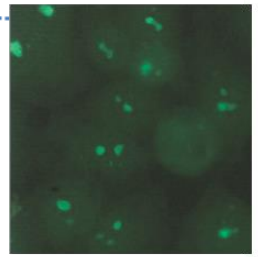


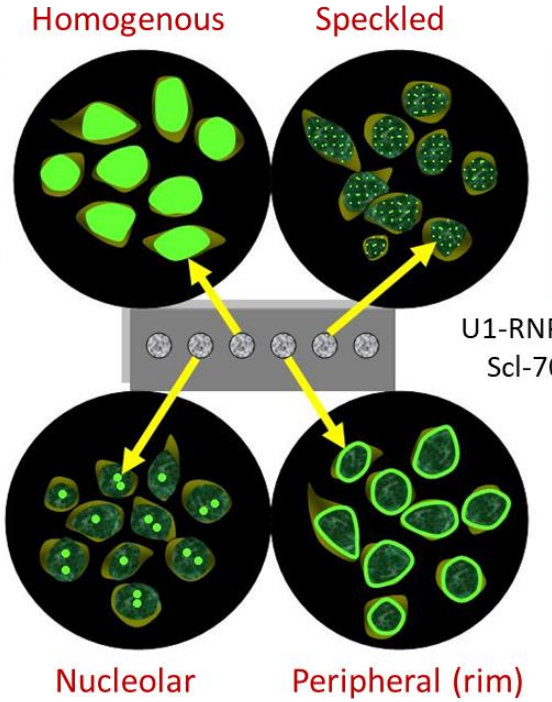
FANA (fluorescent ANA)

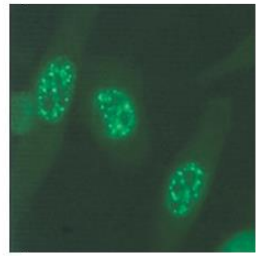


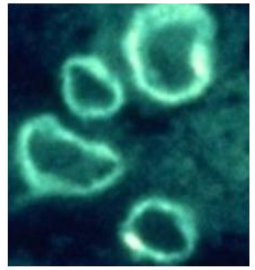


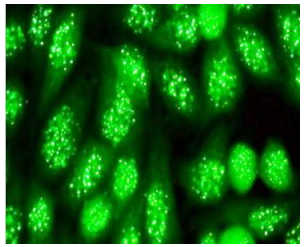

dsDNA, Histones


PM-Scl, RNA polymerase I




U1-RNP, Sm, SSA/Ro, SSB/La, Scl-70, Jo-1, ribosomal-P

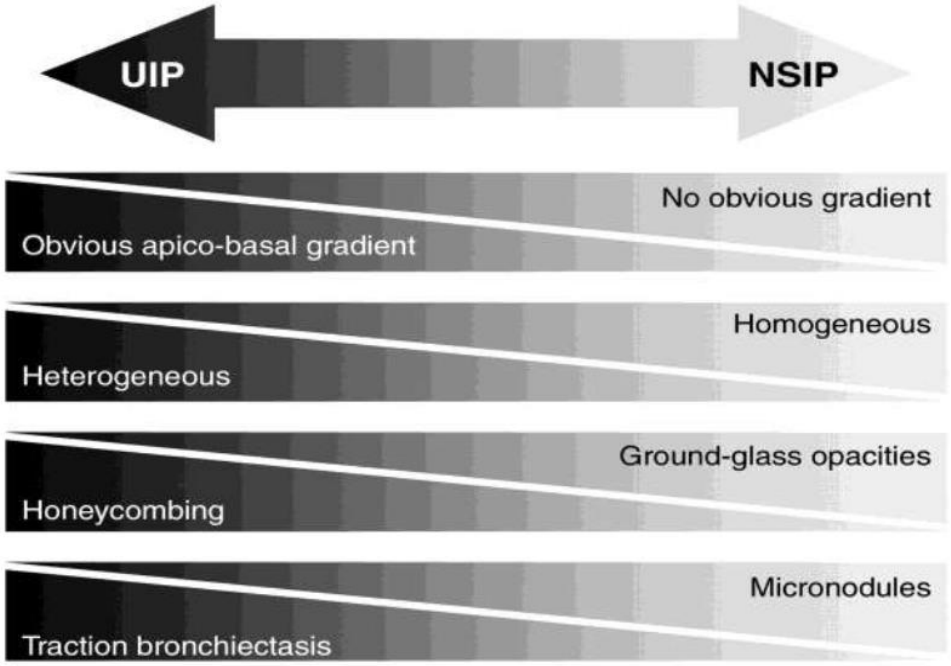

RNP, Sm


Centromere

자가항체의 임상적 의미

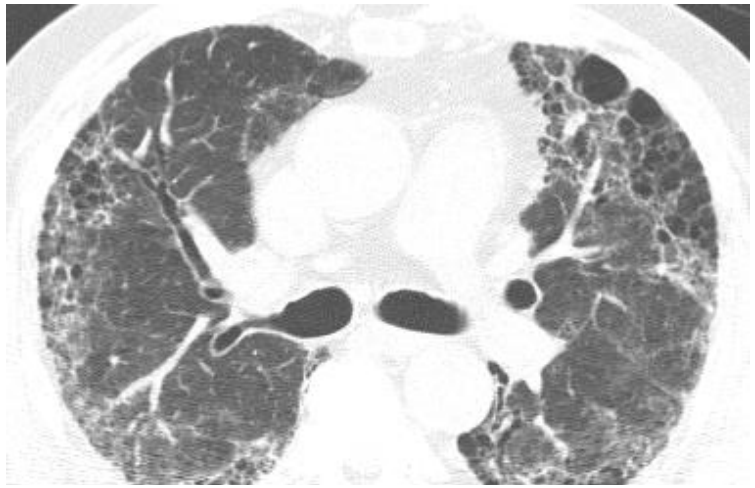
항체	양성률(%)	인지항원	임상적 중요성
항핵항체	98	다양한 핵내 항원	가장 좋은 선별검사; 반복적으로 음성이 나오면 전신홍반루푸스가 아닐 확률이 높음
항dsDNA항체	70	DNA (ds, 이중나선)	고역가는 전신홍반루푸스에 특이적이고 일부 환자에서는 질병활성도, 신장염, 혈관염과 관련됨
항Sm항체	25	6종류의 핵내 U1 RNA와의 복합 단백질	전신홍반루푸스에 특이적임. 명확한 임상적인 관련성은 없음. 대부분의 환자가 항RNP항체를 같이 가짐. 흑인과 동양인에서 백인보다 흔함
항RNP항체	40	U1 RNA와의 복합 단백질	전신홍반루푸스에 특이적이지 않음. 고역가는 전신홍반루푸스를 포함한 몇 가지의 질환이 중복된 양상을 보이는 증후군과 관련. 흑인에서 백인보다 흔함
항Ro(SS-A)항체	30	주로 60 kDa과 hY RNA와의 복합 단백질	전신홍반루푸스에 특이적이지 않음. 건조 증후군, 아급성 피부 루푸스, 선천성 심장차단이 있는 신생아루푸스와 연관이 있음. 신장염 위험성이 감소함
항La(SS-B)항체	10	hY RNA와의 47 kDa의 복합 단백질	항Ro항체와 대개 연관이 있음. 신장염 위험성이 감소함
항히스톤항체	70	히스톤 관련 DNA(뉴클레오솜과 염색질에 존재)	전신홍반루푸스보다는 약물유발루푸스에서 흔히 관찰됨
항인지질항체	50	인지질, β_2-GPI(당단백) 보조인자, 프로트롬빈	세 가지 검사가 이용가능함—카디오리핀과 β_2-GPI(당단백)에 대한 면역효소측정법, 민감한 프로트롬빈 시간(DRWT); 혈전증, 유산, 혈소판감소증의 소인
항적혈구항체	60	적혈구 세포막	직접쿰즈검사로 측정됨. 일부에서 명백한 용혈이 발생
항혈소판항체	30	혈소판의 표면과 변형된 세포질항원	혈소판감소증과 관련이 있으나 민감도와 특이도가 좋지 않음. 임상적으로 유용한 검사는 아님
항신경세포항체 (항Glutamate 수용체 포함)	60	신경세포와 림프구 표면 항원	일부 연구에서 뇌척수액의 양성결과와 활동성의 중추신경계 루푸스과 연관성이 있음
항리보솜P항체	20	리보솜의 단백질	일부 연구에서 혈청의 양성결과와 중추신경계 루푸스에 의한 우울증이나 정신병과 연관성이 있음

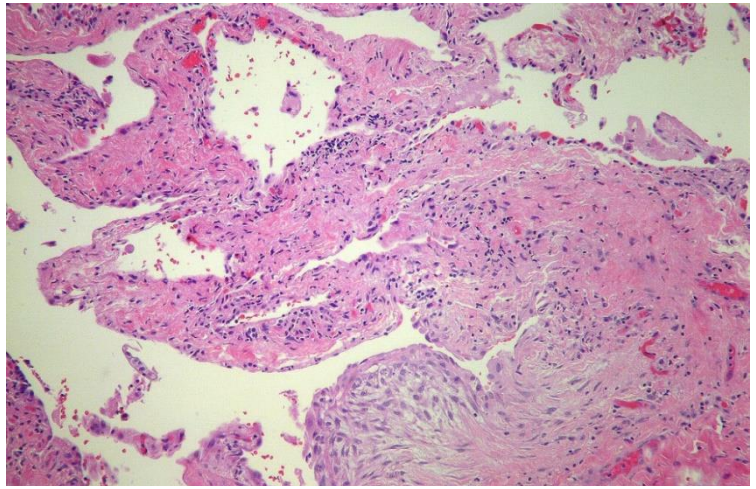
Radiographic and Histologic Pattern of CTD-ILD



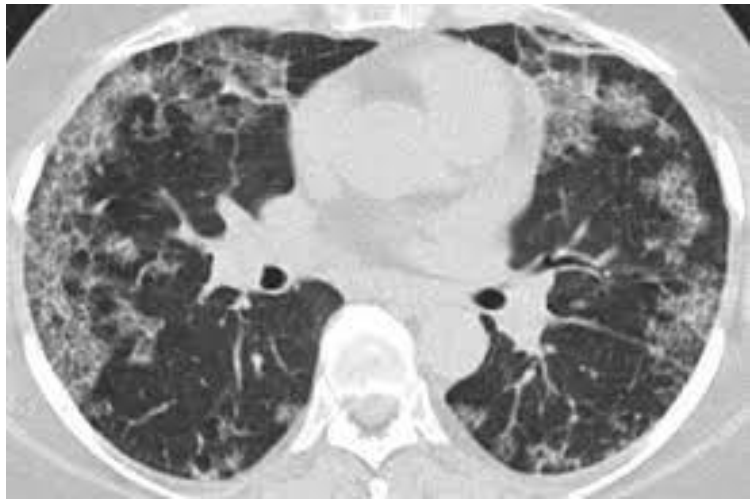
Destructive scarring and/or honeycombing, Fibroblast foci

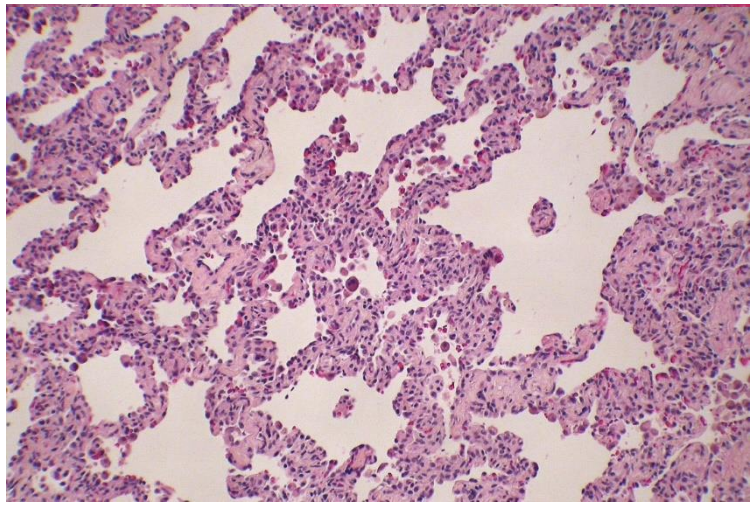
Uniform and diffuse thickening of the alveolar walls is a typical finding in NSIP. alveolar septa thickened by the inflammatory cell infiltrate and mild interstitial fibrosis





UIP: predominant pattern of RA-ILD

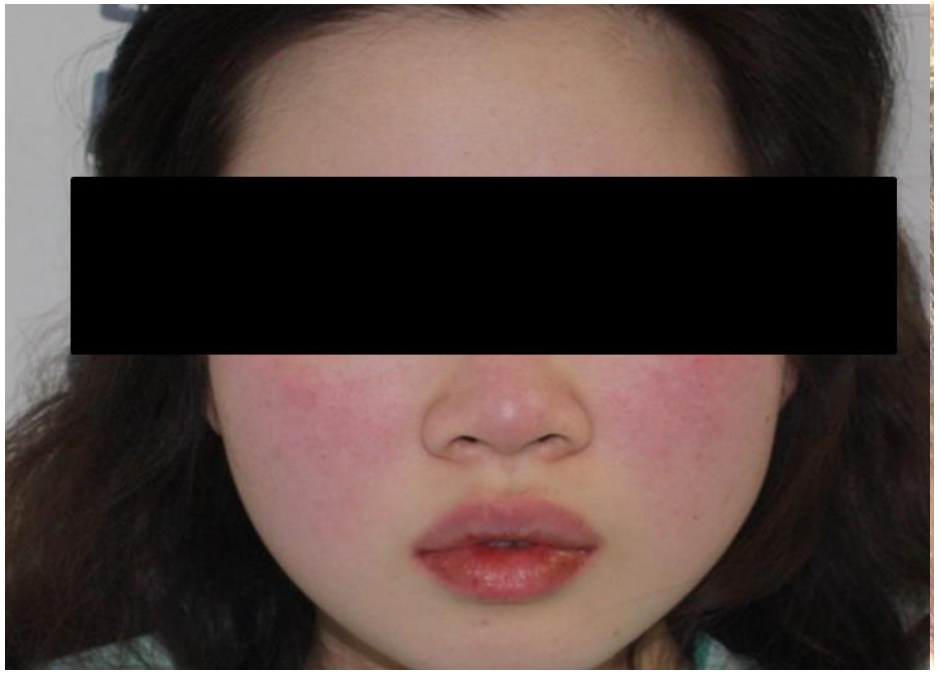




NSIP: m/c type of CTD-ILD, Potentially reversible

Case . 23세, 여자

•**주소:** 점진적 호흡 곤란 (NYHA II), palpitation 호소



검사실 소견:

•ANA+ (1:160) , 보체 감소

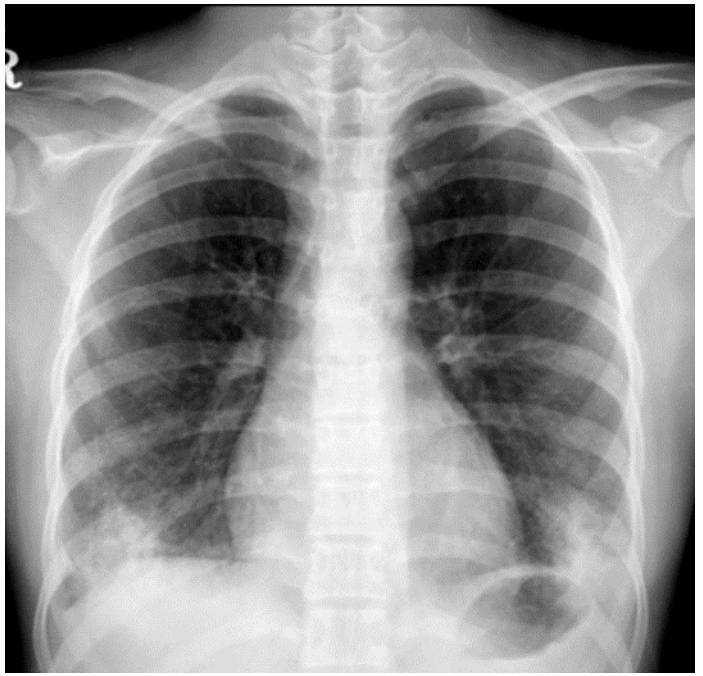
•anti-Sm (-)

•anti-dsDNA IgG/M (+/+)

•anti-Ro (+)

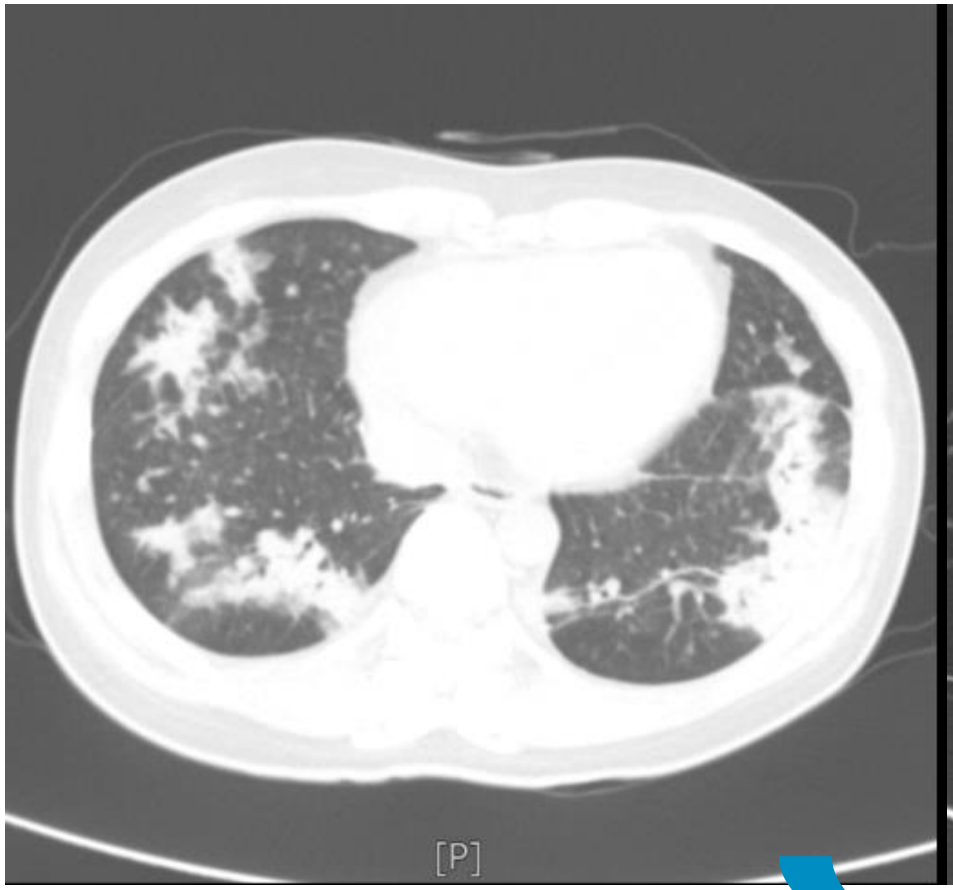
•anti-RNP(-),

•anti-phospholipid Ab (-)

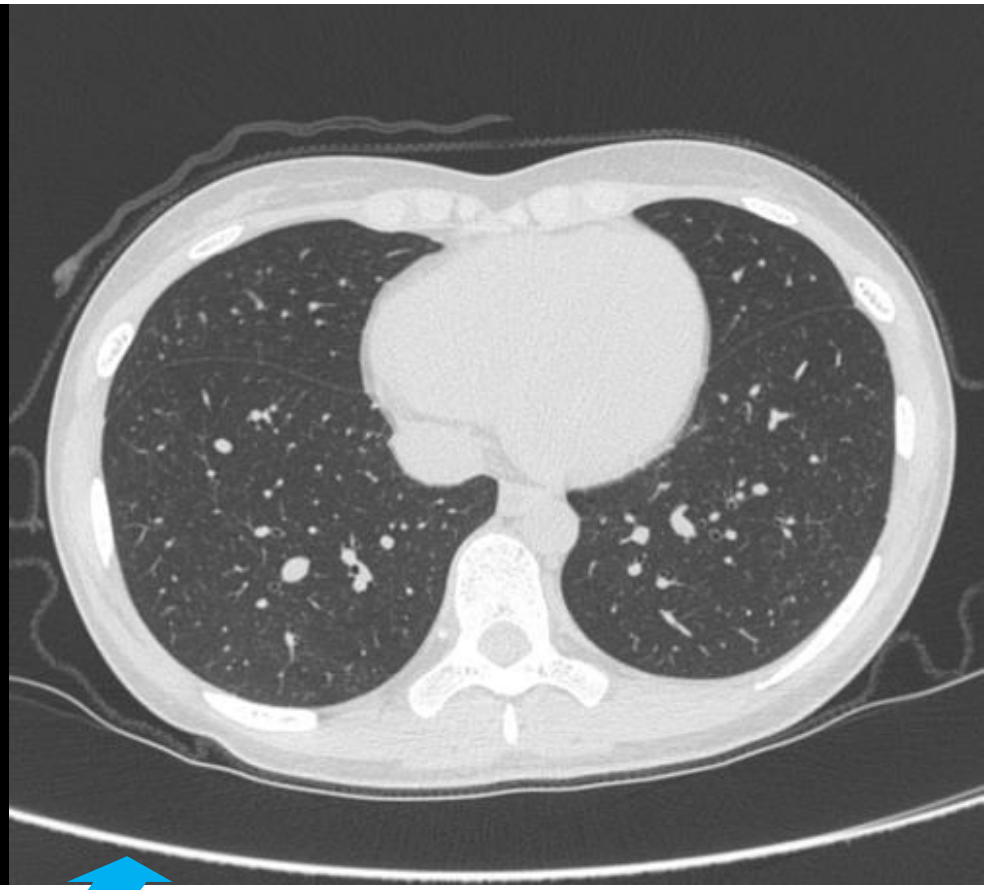


Case . 23세, 여자

2010.02



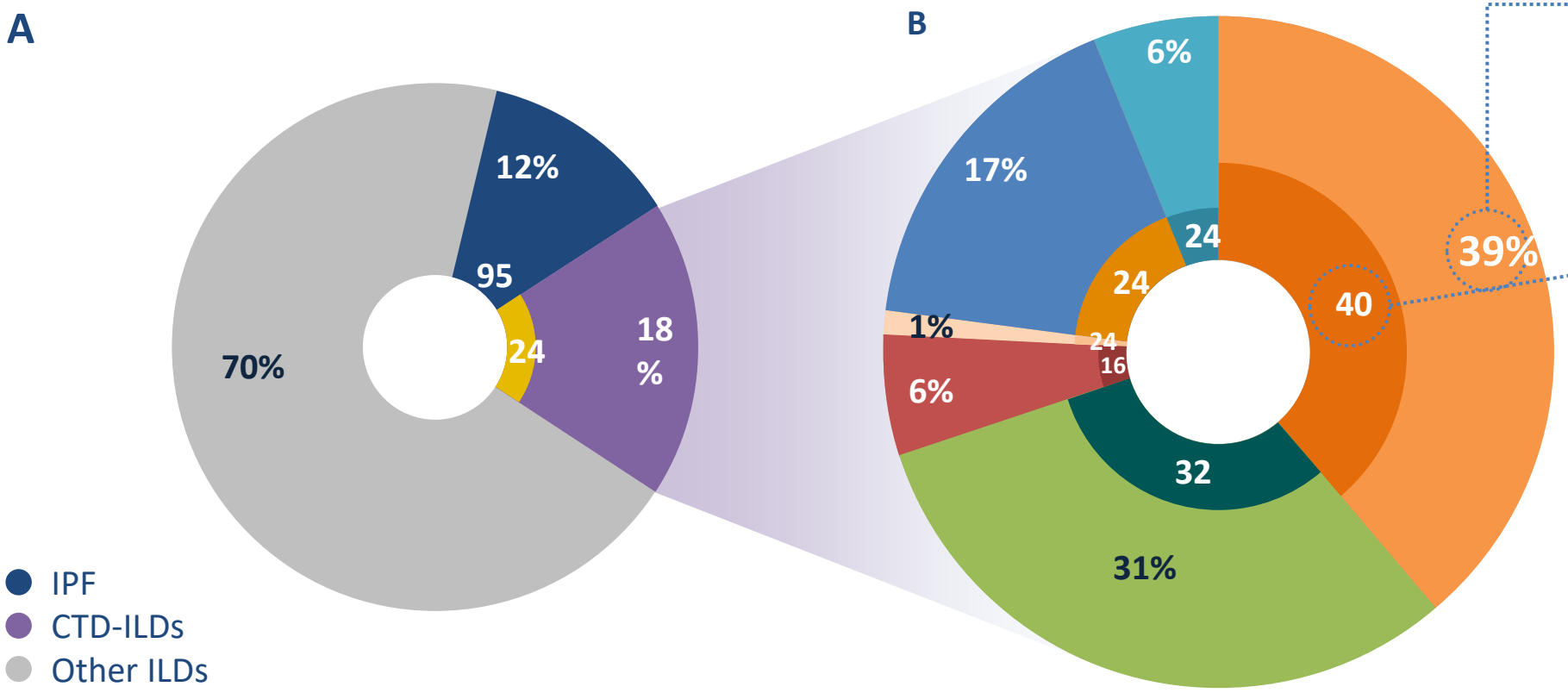
2011.01



• PD 1mg/kg + HCQ 300 mg/day + AZA (2010.03~2011.06)

Up to 40% of CTD-ILD Patients Develop a Progressive Fibrosing Phenotype

- **Relative prevalence of (A) ILDs and (B) CTD-ILDs in Europe and the US**

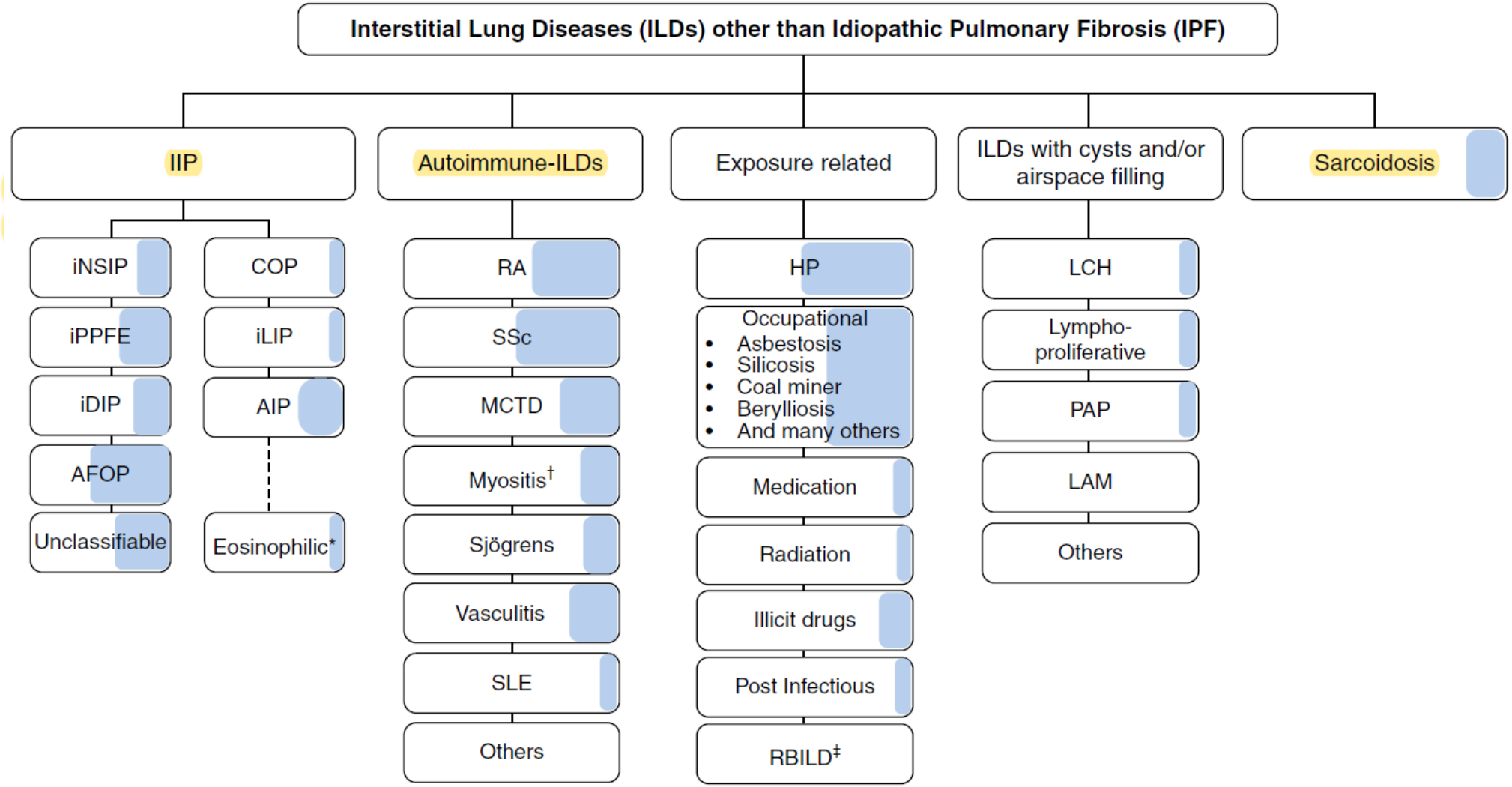


Outer circle values:
Relative prevalence of a given CTD-ILD

Inner circle values:
Estimated proportion of patients with a given CTD-ILD who develop a progressive fibrosing phenotype

Wijsenbeek M et al. N Engl J Med 2020;383:958–68

Up to 40% of CTD-ILD Patients Develop a Progressive Fibrosing Phenotype



G Raghu et al. Am J Respir Crit Care Med 2022; 205(9); e18–e47.

Pathogenesis and Development of CTD-ILD

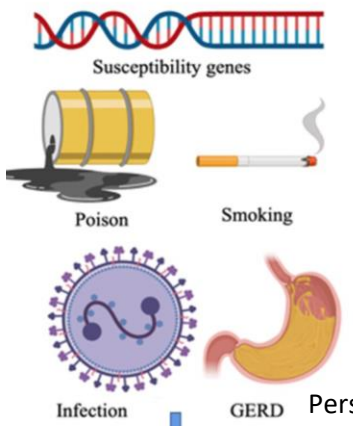
Initiation
Epithelial damage
Endothelial activation
Immune-cell infiltration
Inflammation

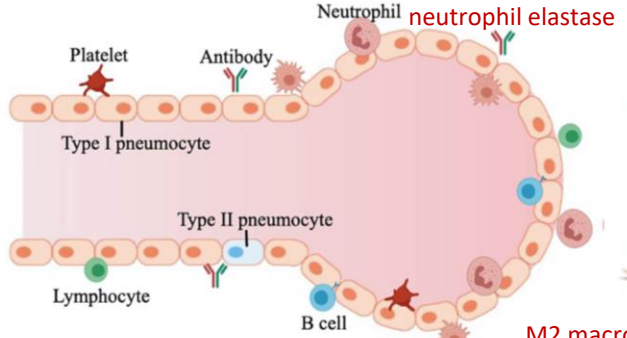
Progression
Fibroblast proliferation
Fibrocyte recruitment
Epithelial–mesenchymal transition
Ongoing epithelial damage

Failed resolution
Myofibroblast persistence
Altered matricellular interaction
Perturbed epithelial repair
Ongoing epithelial damage

Nat Rev Rheumatol 2014;10(12):728-39.

Risk factor
- Smoking
- Periodontitis
- Infection
- Dysbiosis
- GERD
- Genetic susceptibility

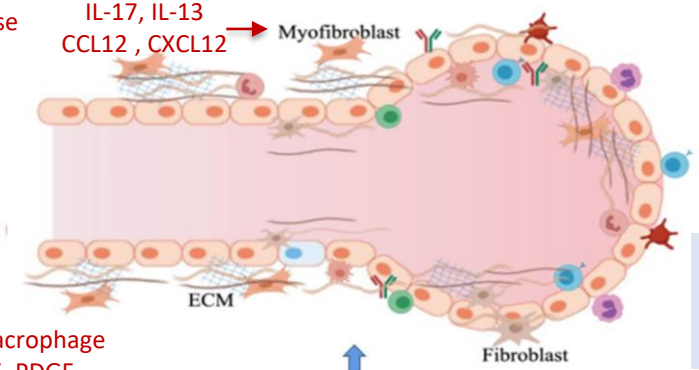




MMPs, TIMPs
neutrophil elastase

ACPA

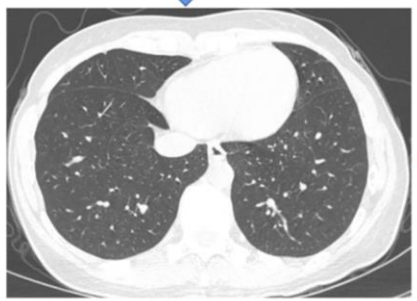
M2 macrophage
→ TGF, PDGF

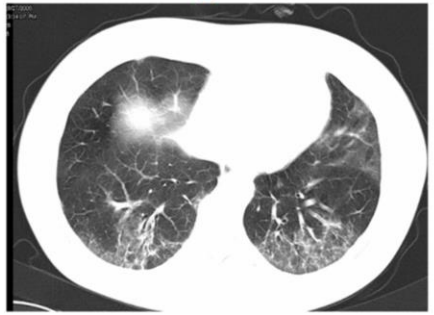


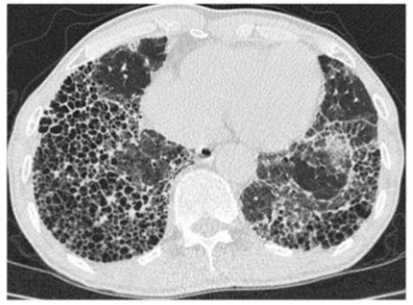
Self-Perpetuating Fibrosis Loop

Persistent and repeated damage to epithelial cells, leads to the activation of immune cells

prolonged inflammation leads to alveolar and peribronchial wall proliferation, and an abnormal fibrotic repair process leads to the excessive ECM by myofibroblast

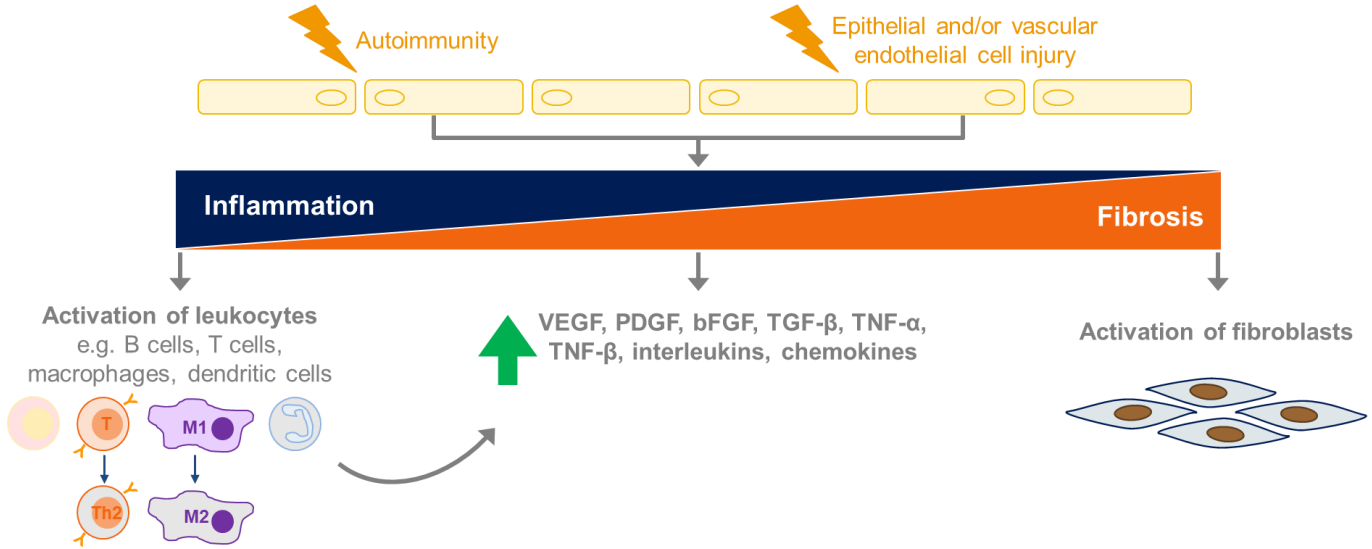

Normal lung

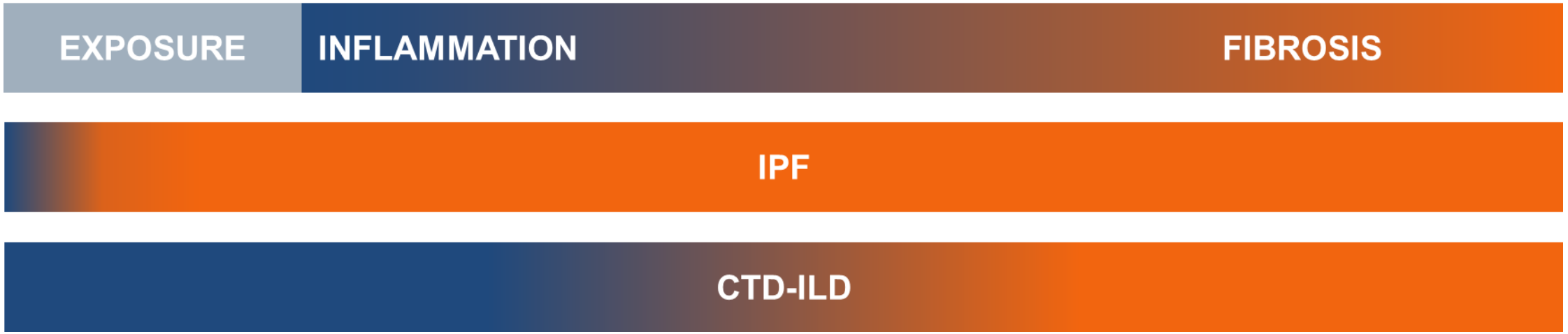

Inflammatory ILD pattern


Fibrotic ILD pattern

Shao T et al. Front Immunol. 2022;12:684699.

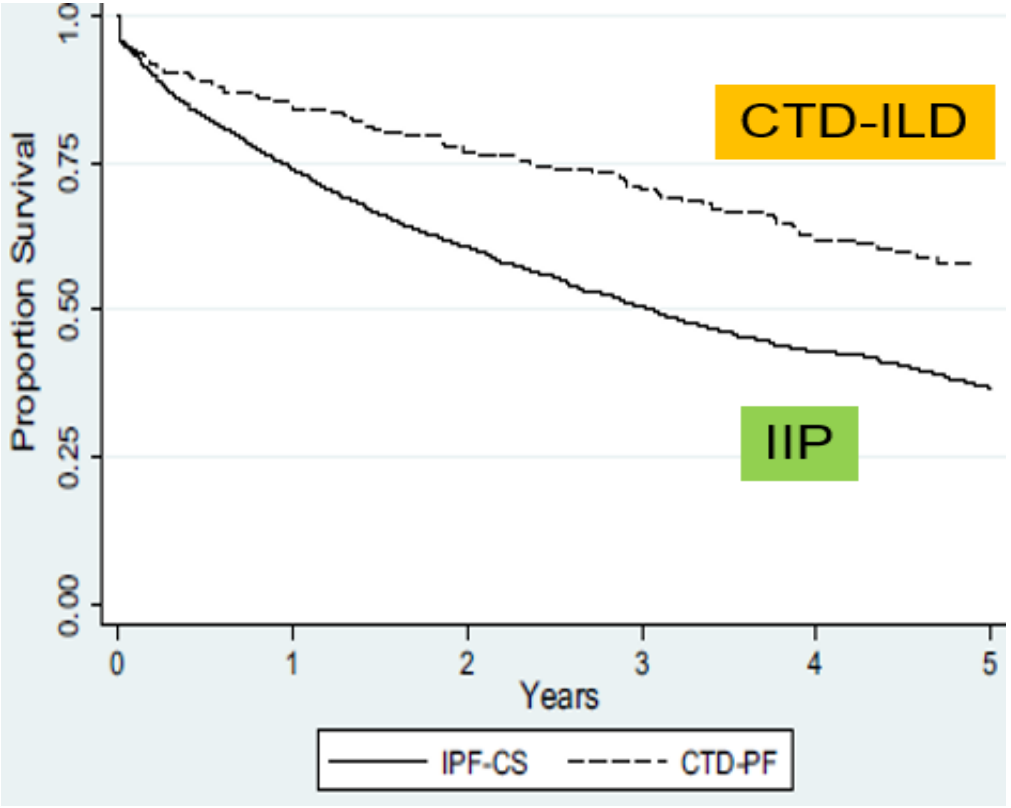
Pathogenesis of PPF
: Interplay of Inflammation and Fibrosis





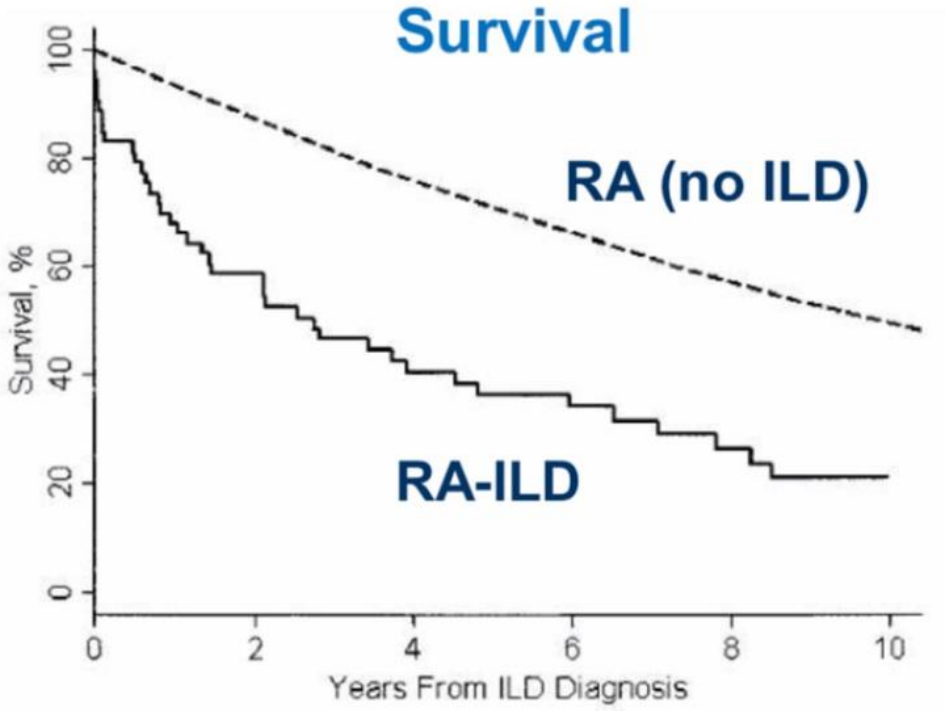
Wells AU, Denton CP. Nat Rev Rheumatol 2014;10:728-739; Wongkarnjana A et al. Curr Opin Pulm Med 2020;26:436–442.

Prognosis : CTD-ILD is Better than IIP



Navaratnam et al. Respir Med. 2011

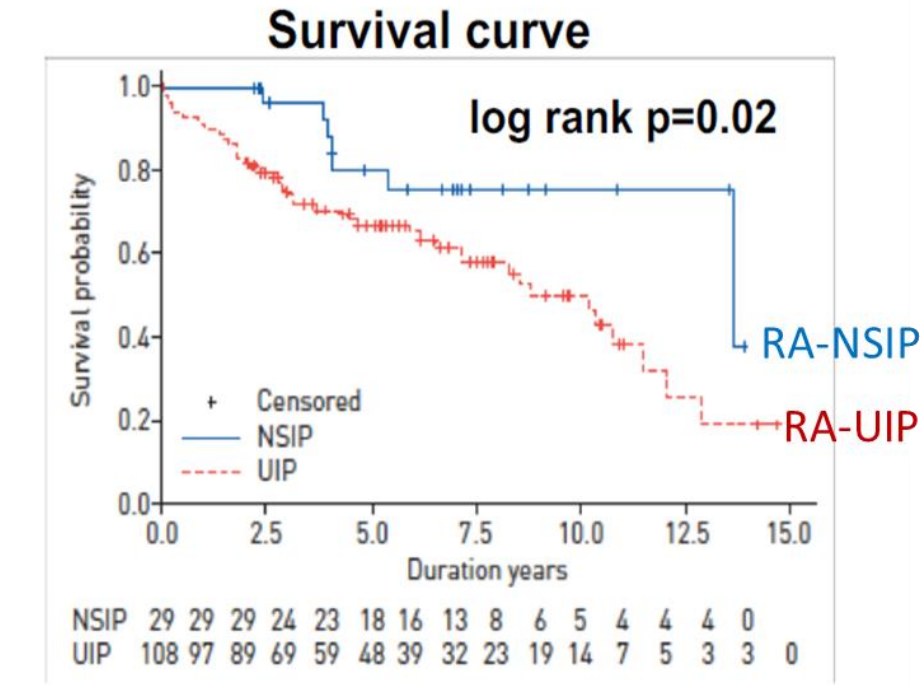
- Prevalence of ILD in RA : 10-58%, UIP pattern : more common
- 10-20% ILD precedes articular disease, No correlation with severity
- Responsible for 10-20% of deaths in RA patient: 2nd m/c reason



Bongartz et al. Arthritis Rheum 2010;62:1583-91,
Doyle et al. Am J Respir Crit Care Med 2015; 191:1403-11

Prognosis: Significance of Histologic Pattern

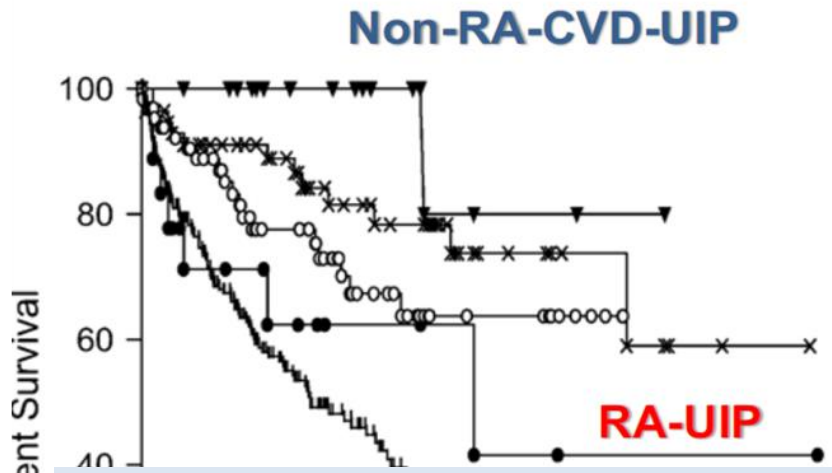
- 108 had UIP on HRCT (RA-UIP) and 29 had NSIP on HRCT (RA-NSIP)



median survival UIP10.2 vs NSIP13.6(years)

Solomon JJ, et al.Eur Respir J. 2016;47(2):588

- IIP n= 269, CTD n=93
- Survival : IPF-UIP ≒ RA-UIP < non-RA-CTD-UIP



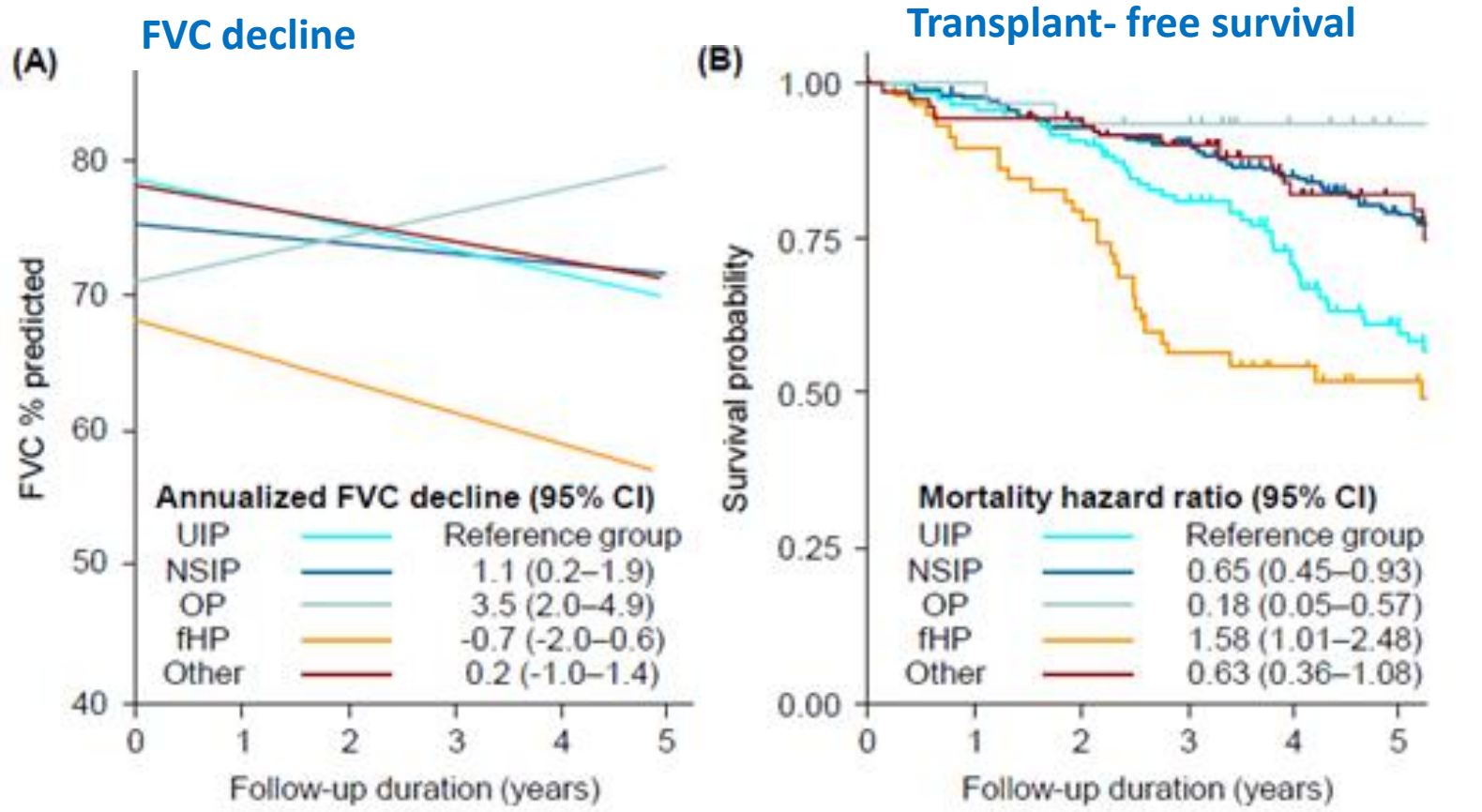
[Pathologic Difference of RA-UIP]

- Less fibroblastic foci
- More inflammatory cell infiltration such as germinal centers

→ Anti-inflammatory medication is potentially effective for Tx of RA-UIP

Chest. 2005 Jun;127(6):2019

Prognosis: Significance of Image Pattern in CTD-ILD

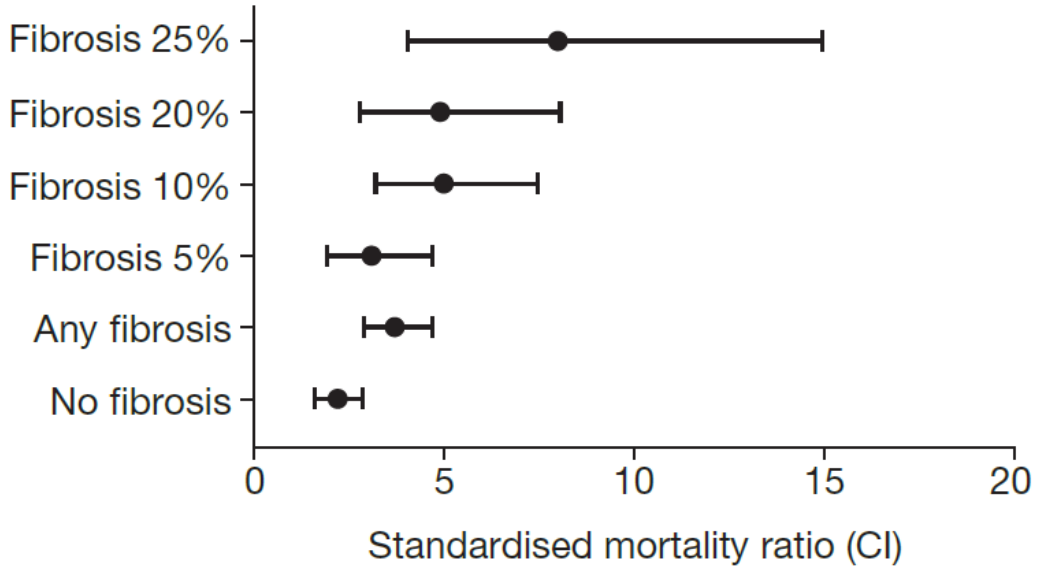


- Patients with NSIP and OP had less decline in FVC% predicted **(Figure 1A)** and lower mortality **(Figure 1B)** than patients with UIP

Zheng B, et al. EULAR 2023 , POS0123

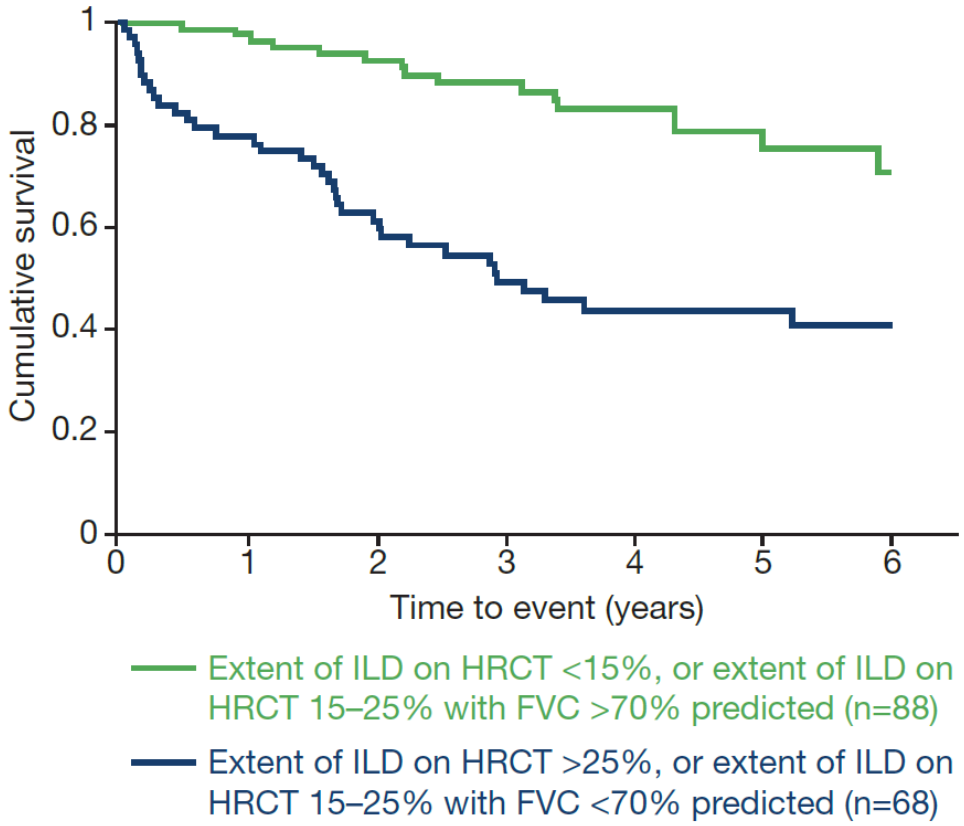
Prognosis : Significance of Extent of Fibrosis

Standardised mortality ratios* by extent of lung fibrosis in a Norwegian cohort of patients with SSc-ILD (n=630)[1]



*versus subjects from general population matched by sex, age, year of birth, area of residence.

Survival by extent of lung fibrosis in patients with RA-ILD at two UK centres[2]



Goh NS, et al. Am J Respir Crit Care Med. 2008;177:1248-1254

Lung Function Trajectory of in RA-ILD

KOrean Rheumatoid Arthritis Interstitial Lung disease (KORAIL) Cohort

Subjects

RA according to 2010 ACR classification criteria

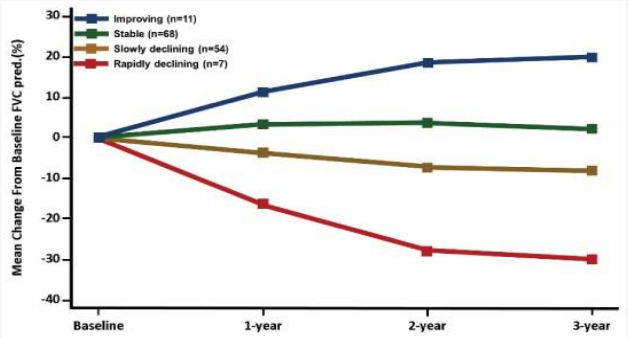
ILD diagnosed by chest CT scan

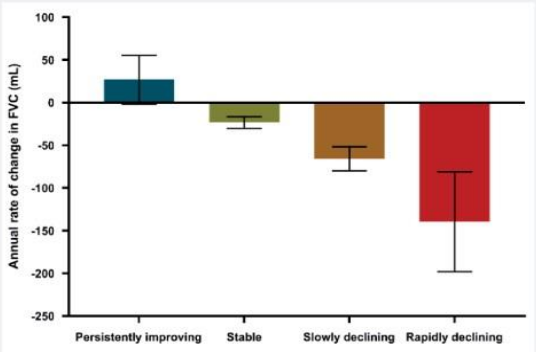
Methods

A prospective observational cohort study

	Baseline	1-year	2-year	3-year
	V1	V2	V3	V4
Pulmonary function test	√	√	√	√
RA disease activity	√	√	√	√

Results





X 10-fold

Risk of Rapidly declining lung function

Old age ≥70-year-old

Early RA diagnosed within the preceding 2 years

		Trajectory group of DAS28-ESR			
		Maintaining LDA	Improving	Worsening	Persistently HDA
Trajectory group of FVC% pred.	Persistently improving	3 (5.4%)	3 (5.8%)	4 (19.0%)	0 (0.0%)
	Stable	31 (55.4%)	23 (44.2%)	10 (47.6%)	3 (60.0%)
	Slowly declining	21 (37.5%)	25 (48.1%)	5 (23.8%)	1 (20.0%)
	Rapidly declining	1 (1.8%)	1 (1.9%)	2 (9.5%)	1 (20.0%)
	Total	56 (100%)	52 (100%)	21 (100%)	5 (100%)

Conclusion

- Eighty-seven percent of patients with RA-ILD experience stable or slowly declining lung function.
- Lung function trajectory is not comparable with the RA disease activity trajectory.
- Old age, early RA, and simultaneous diagnosis of RA and ILD increased poor outcomes.

Chang SH, et al. Rheumatology (Oxford). 2023 Jan 25;kead027.

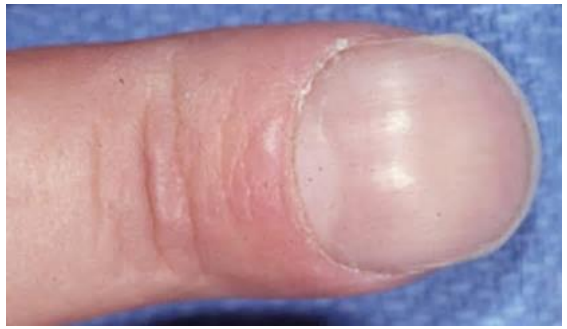
Dignostic Considerations of CTD-ILD

- Symptoms and Signs Suggesting CTD Existence
- Biomarkers
- Monitoring Algorithm

Clinical Clues Suggestive of Concomitant CTD

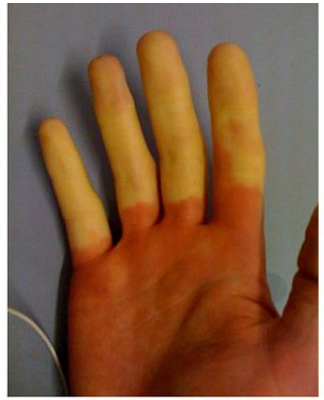
ILD 의심

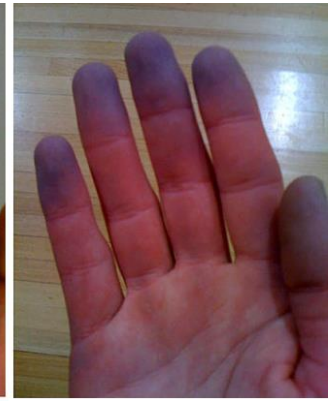
- Shortness of breath with activities
- Cough : a dry, hacking cough that never goes away
- Fatigue, Weakness
- Pleuritic chest pain
- Poor appetite and weight loss
- Clubbing (rounding) of fingers and toes

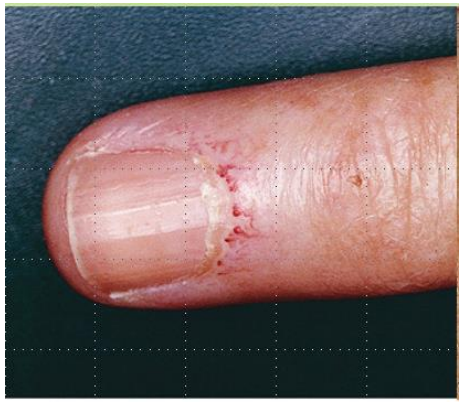


CTD 의심

- 레이노현상, 혈관 확장, 수지궤양
- 피부발진
- 관절부종 및 압통
- 근육통이나 근위약감
- 안구 및 구강 건조





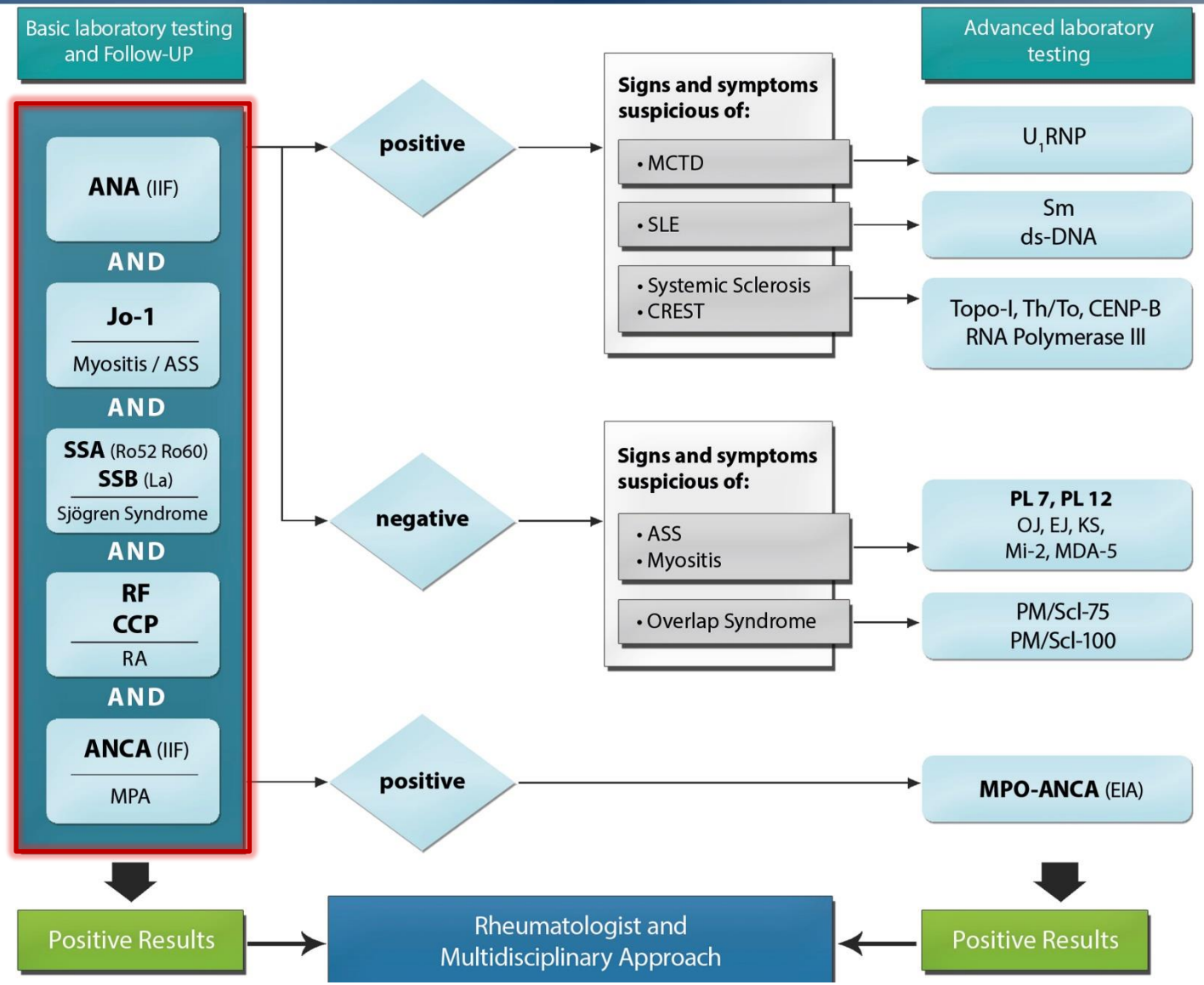


- In ILD, ↓ FVC often occurs w/ proportional ↓ in DLCO (FVC/DLCO ~ 1.0)
- FVC/DLCO > 1.6 → Concern for PAH

Risk Factors for CTD-ILD

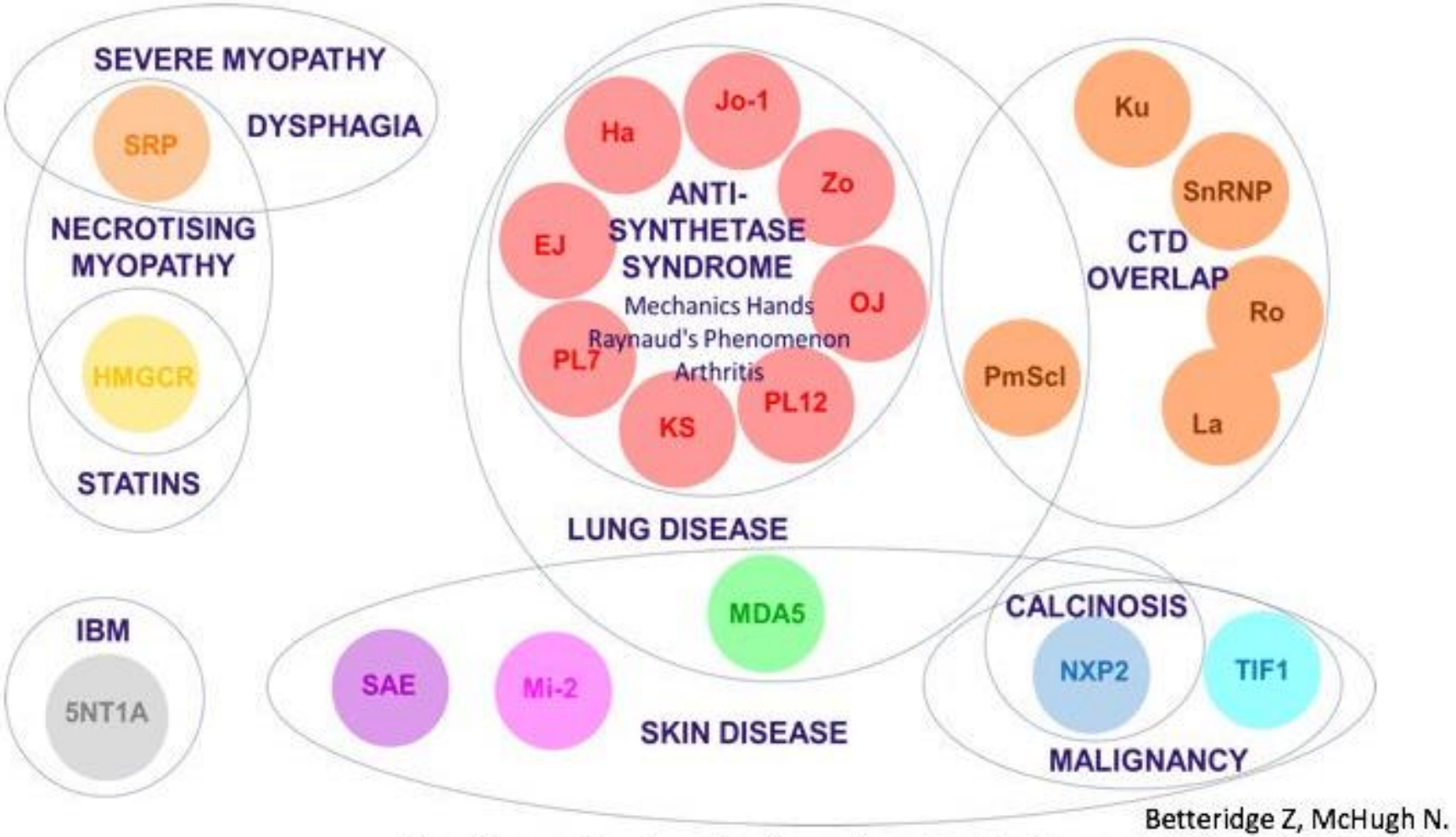
RA-ILD Progression

Suggested AutoAb Screening Test for ILD



Thomas Bahmer et al.
Respir Med. 2016;113:80-92

Myositis Specific AutoAbs



Betteridge Z, McHugh N.
Myositis-specific autoantibodies: an important tool to support diagnosis of myositis.
J Intern Med. 2016 Jul;280(1):8-23

Case . F/45, Rapidly Progressive ILD in anti-MDA5+ CADM

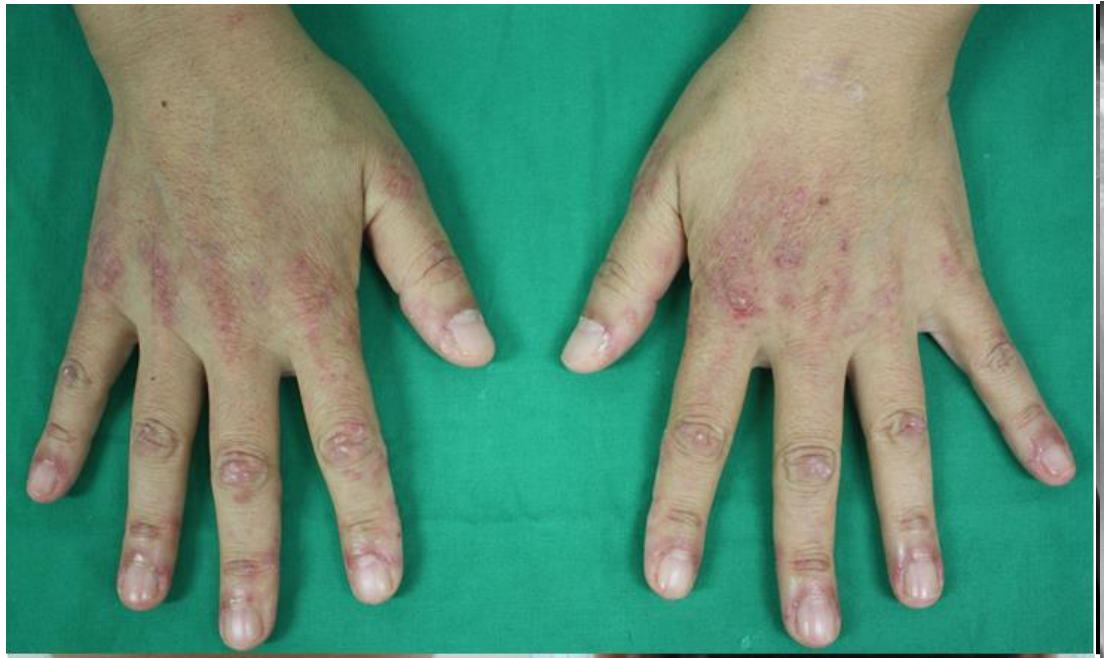
주소: 호흡곤란

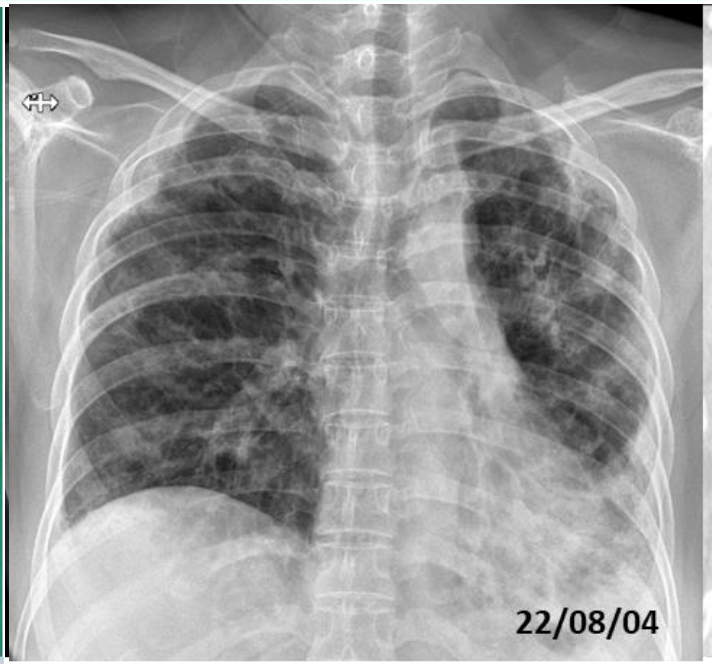
병력:

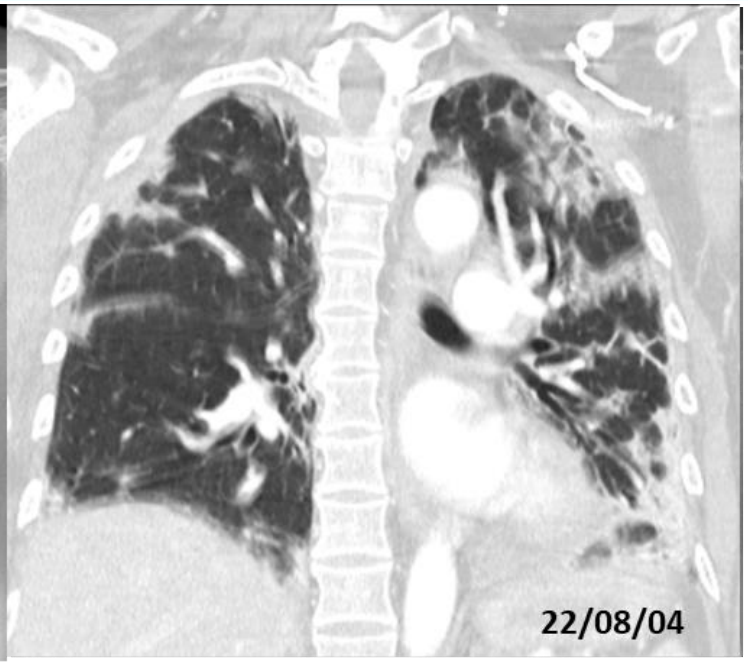
- 22.2월 말 좌측 눈꺼풀 부종과 발적 발생,
- 22.3월 COVID-19 확진, 이후 양 어깨 근육통 및 호흡곤란 시작,
- 22.4월 타 병원 입원, Dermatomyositis with ILD 진단 후 약물치료 시작.
- 22. 6. 27~7.12 호흡곤란 악화로 재입원 후 약물 조정하였으나 숨찬 증상 지속
- 22.7.31 본원 방문. 검사와 치료 위해 입원 함.

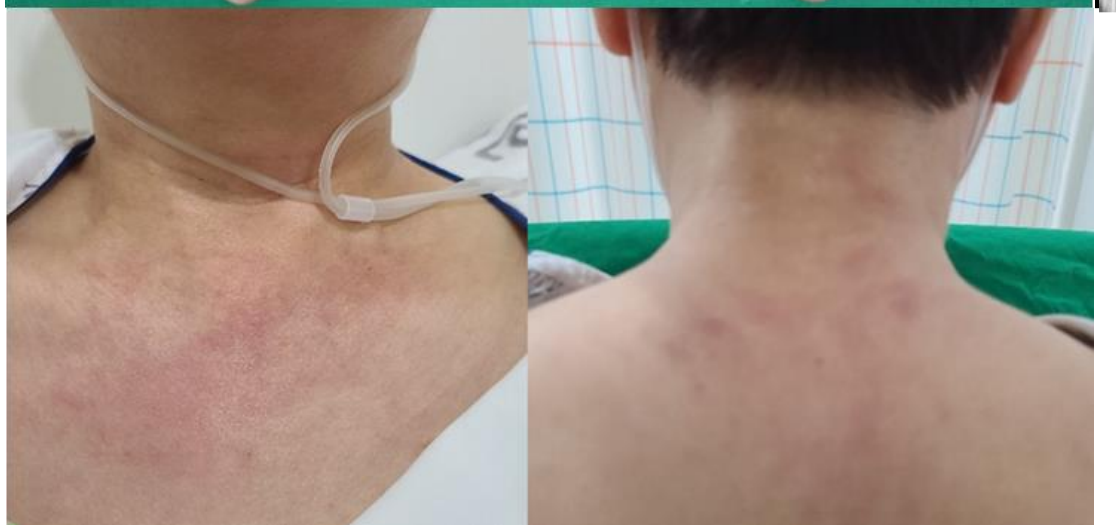
- ROS : 근 위약감-, 근육통-, 호흡곤란 (NYHA III) , 기침-, 가래- , 레이노 +
- P/Ex: MMT-8 113/150 (Gluteus maximus/medius 근력 감소)
- CK 26, LD 286, AST/ALT 41/40, Aldolase 8.4
- ESR 120, CRP < 0.5
- ANA 음성, anti-Jo1 음성

Case . F/45, Rapidly Progressive ILD in anti-MDA5+ CADM









EUROLineScan - Evaluation

Page 1 of 1

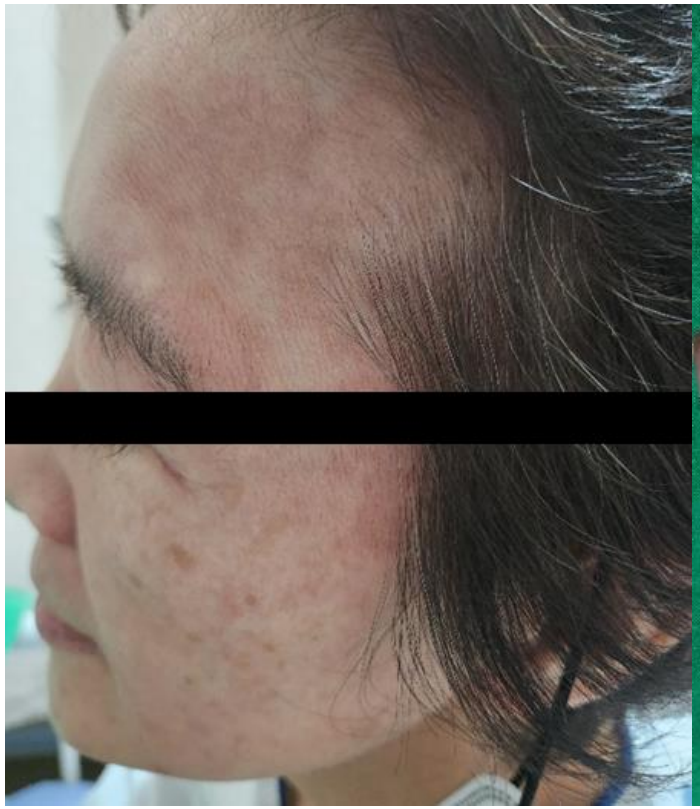
Protocol: 20220805-3 Date: 2022-08-05
Operated by: Administrator Printed: 2022-08-05

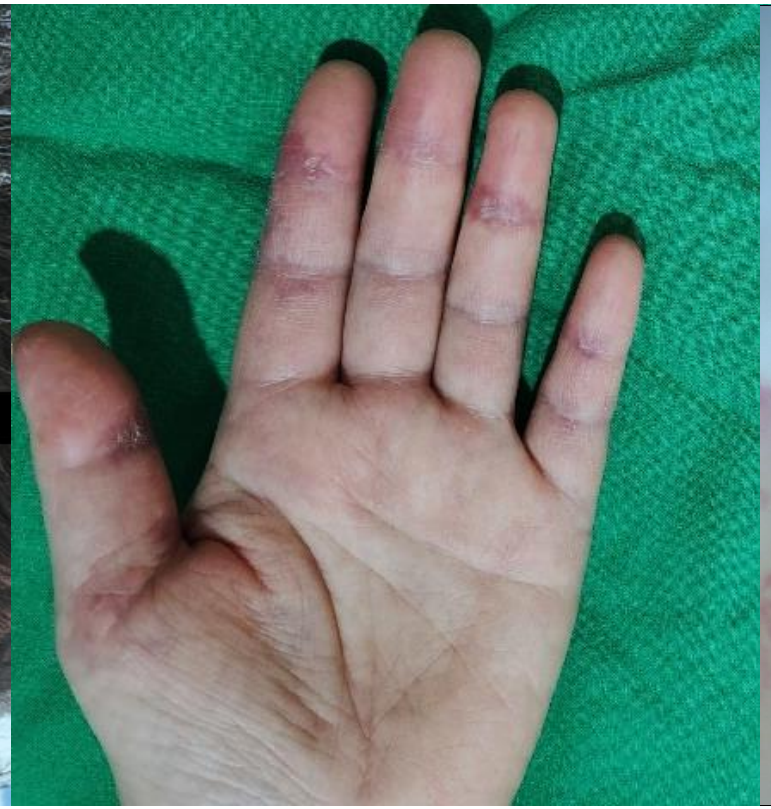
No	Patient ID / Patient name / Sent from / Test / Lot / Gender / Age	EUROLINE / Allergy / EUROASSAY	Westernblot
		Abbreviation / *Intensity* / Char	Results / Result — Abbreviation / *Intensity* / Char
1	KHMC		

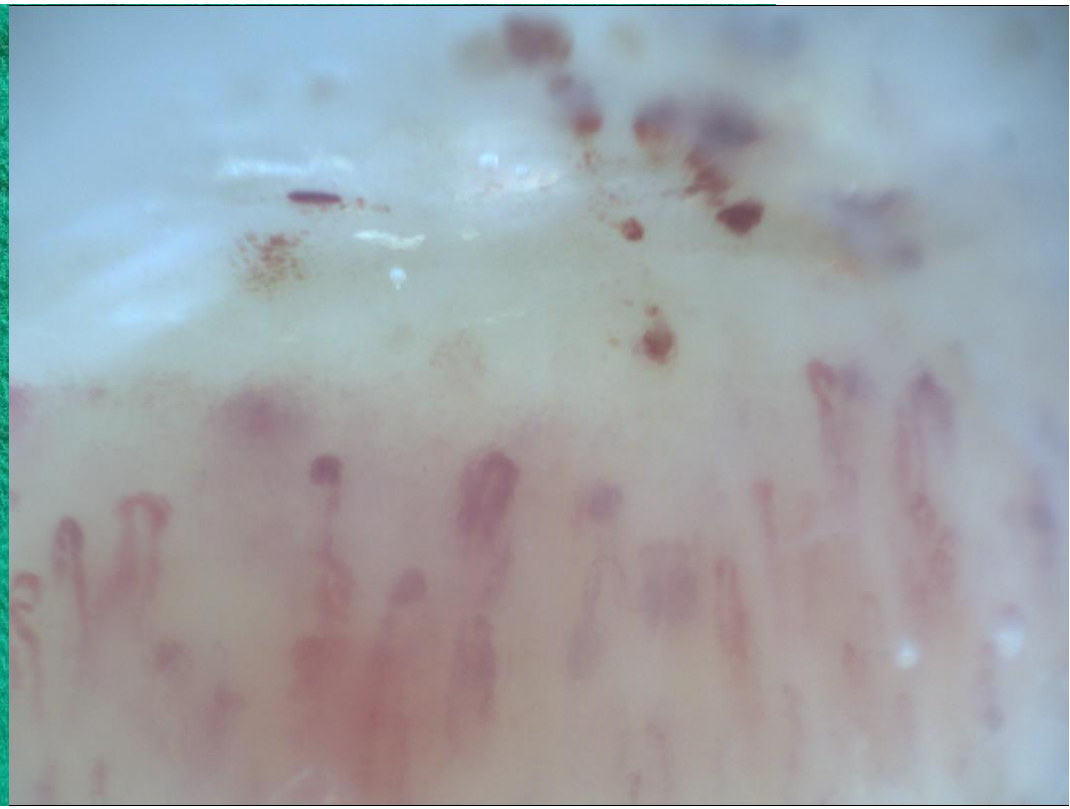
	La	Co	Ro52	OJ	EJ	PL-12	PL-7	SRP	Jo-1	PM75	PM100	Ku	SAE1	NXP2	MDA5	TIF1g	Mi-2b	Mi-2a
Myositis-EL_4	-1	130	94	1	1	16	4	1	2	2	1	0	0	1	58	0	1	1
Myo-EL_4	o	+++	+++	o	o	+	o	o	o	o	o	o	o	o	+++	o	o	o
Unknown																		

Case . F/57, Rapidly Progressive ILD in anti-MDA5+ CADM

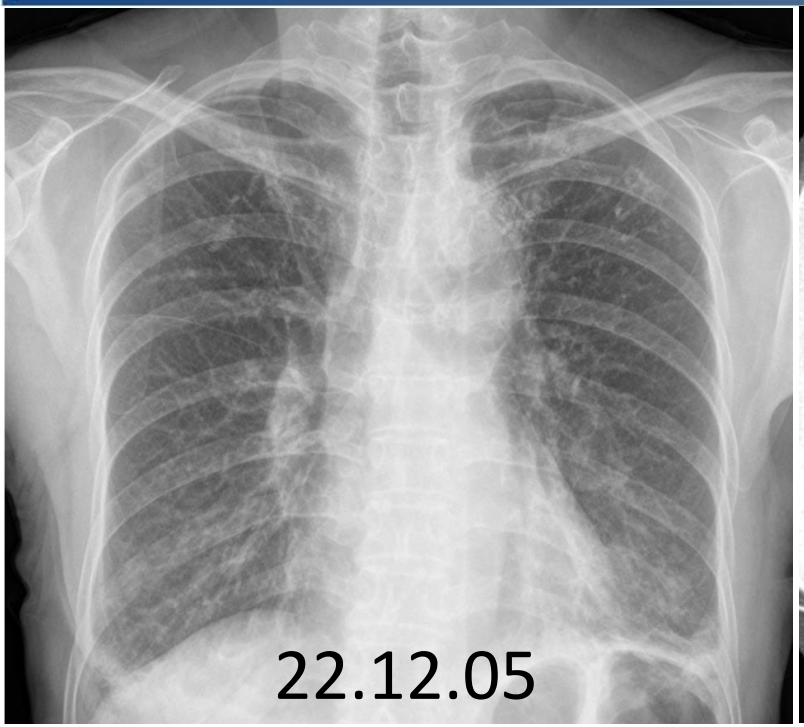
- 5개월 전부터 손등, 얼굴 , 눈꺼풀 등에 홍반성 발진과 소양감 발생.
- ROS : 근위약감-, 근육통-, 호흡곤란 (NYHA I), 기침+, 가래-, 레이노 +
- P/Ex: MMT-8 144/150 (Hand grip 약화 외에 근위약감 관찰되지 않음)

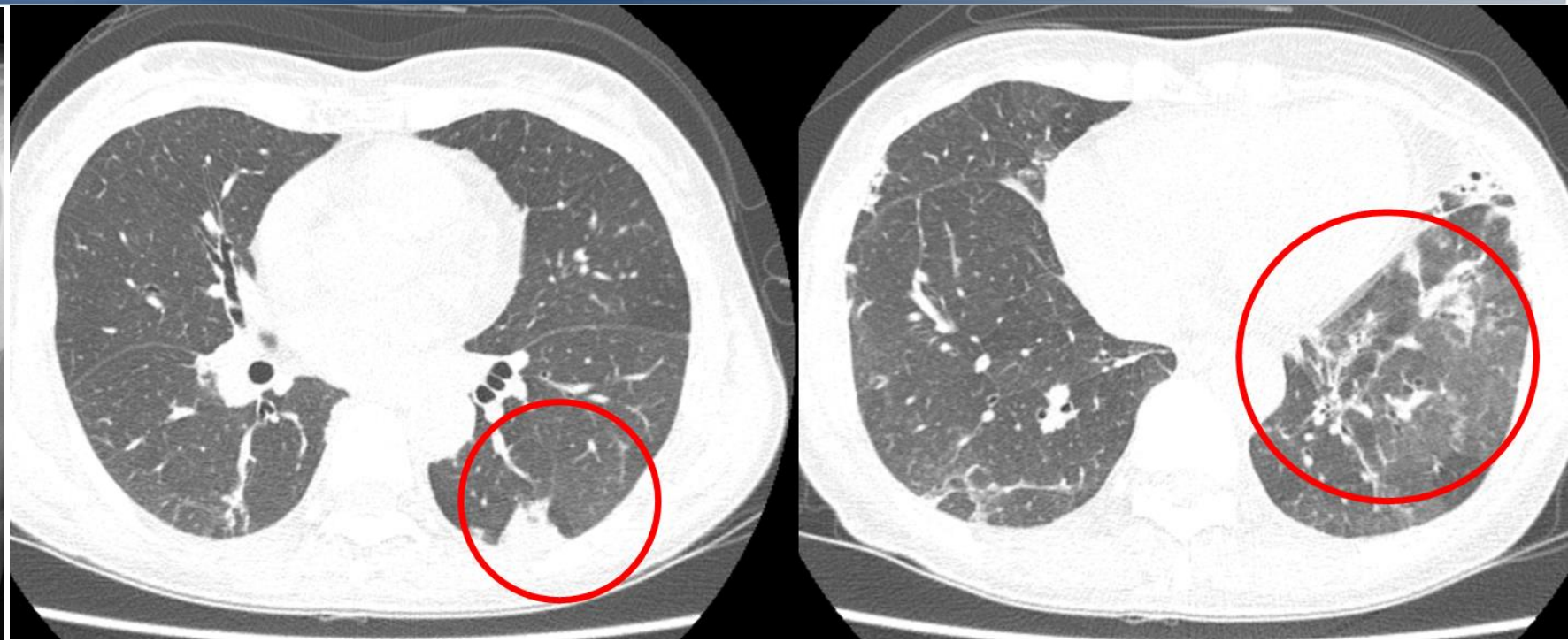






Case . F/57, Rapidly Progressive ILD in anti-MDA5+ CADM





MYO 4/ 25-12

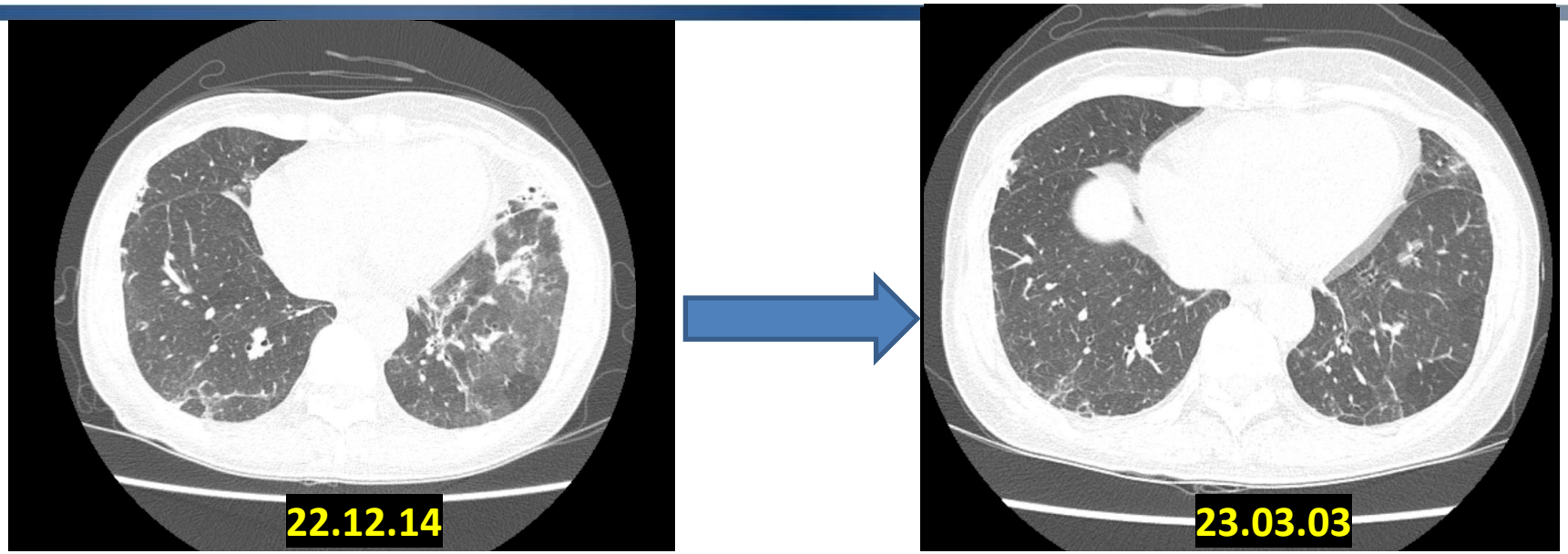
Antigen	Intensity	Class
Mi-2alpha (Mi-2a)	1	o
Mi-2beta (Mi-2b)	0	o
TIF1gamma (TIF1g)	1	o
MDA5 (MDA5)	38	++
NXP2 (NXP2)	1	o
SAE1 (SAE1)	1	o
Ku (Ku)	0	o
PM-Scl100 (PM100)	0	o
PM-Scl75 (PM75)	1	o
Jo-1 (Jo-1)	1	o
SRP (SRP)	1	o
PL-7 (PL-7)	1	o
PL-12 (PL-12)	1	o
EJ (EJ)	80	+++
OJ (OJ)	1	o
Ro52 (Ro52)	28	++
Control (Co)	54	+++

Anti-MDA5 2+. Anti-EJ 3+, Anti-Ro52 2+

- CK 231, LD 407, AST/ALT 104/58, Aldolase 11.3
- CRP < 0.5, ESR 84
- ANA Cytoplasmic (1:160), Anti-Jo-1: Negative
- KL-6 1173 ▲

- PFT: FVC 58%, %, FEV1/FVC 73%, DLCO 49%
- 6분 도보 검사 : Desaturation 87% (1'30"), 303M

Case . F/57, Rapidly Progressive ILD in anti-MDA5+ CADM



CYC 500mg pulse Tx q 2 weeks * 6 Cycles	**IVIG 0.5g/kg /d * 4days #1 (1/4-7), #2((2/1-4) , #3(3/1-4)**	**Tacrolimus 2mg/day**

Prednisolone 1mg/Kg…. → 0.5mg/Kg…. → 15mg/day

2022.12.15 : FVC 58 %, FEV1/ FVC 78 %, DLCO 49 %, 6min WT: 303m, 87 %

2023.01.31 : FVC 78%, FEV1/ FVC 78 % DLCO 57 %, 6min WT: 276m, 95%

2023.02.28 : FVC 63%, FEV1/ FVC 73% DLCO 55%, 6min WT: 370m, 99%

*Advanced-stage (FVC% < 50% or unable to perform PFTs): mortality ~70%

PFTs Provide Information on ILD & PAH

	Patient 1 Normal	Patient 2 Evolving PAH?	Patient 3 Suspect PAH	Patient 4 Severe ILD	Patient 5 ILD + PAH?
FVC %	80	80	70	40	40
DLco %	80	60	35	40	20
Ratio	1	1.3	2	1	2

- In ILD, ↓ FVC often occurs w/ proportional ↓ in DLCO (FVC/DLCO ~ 1.0)
- FVC/DLCO > 1.6 → Concern for PAH

Biomarkers of CTD-ILD

- **KL-6 :** correlates with RA-ILD severity
- **HSP 90/70 :** more specific for RA-ILD
- ***MUC 5B*** **:** most common genetic variant in RA-UIP, not so in systemic sclerosis or other CTD-ILD
- **MMP7**
- **SNPs in telomere-related genes :** Similar associations in RA-UIP and IPF
- **CXCL10**
- **Cancer markers (CA19-9, CA 125)**

Biomarkers with Lung Involvement in RA-ILD

KOrean Rheumatoid Arthritis Interstitial Lung disease (KORAIL) Cohort

Table 2. Correlations between FVC and DLCO and serum cytokines and biomarkers

	TNF-α	IL-6	MMP-7	SP-D	KL-6
FVC					
r_s	−0.074	−0.085	−0.267	−0.250	−0.223
p-value	0.368	0.305	0.001	0.002	0.006
DLCO					
r_s	−0.127	−0.063	−0.404	−0.286	−0.226
p-value	0.131	0.454	0.000	0.001	0.007

FVC: forced vital capacity, DLCO: diffusing capacity for carbon monoxide, TNF-α : tumor necrosis factor α , IL-6: interleukin 6, MMP-7: matrix metallopeptidase 7, SP-D: surfactant protein D, KL-6: Krebs von den Lungen 6.

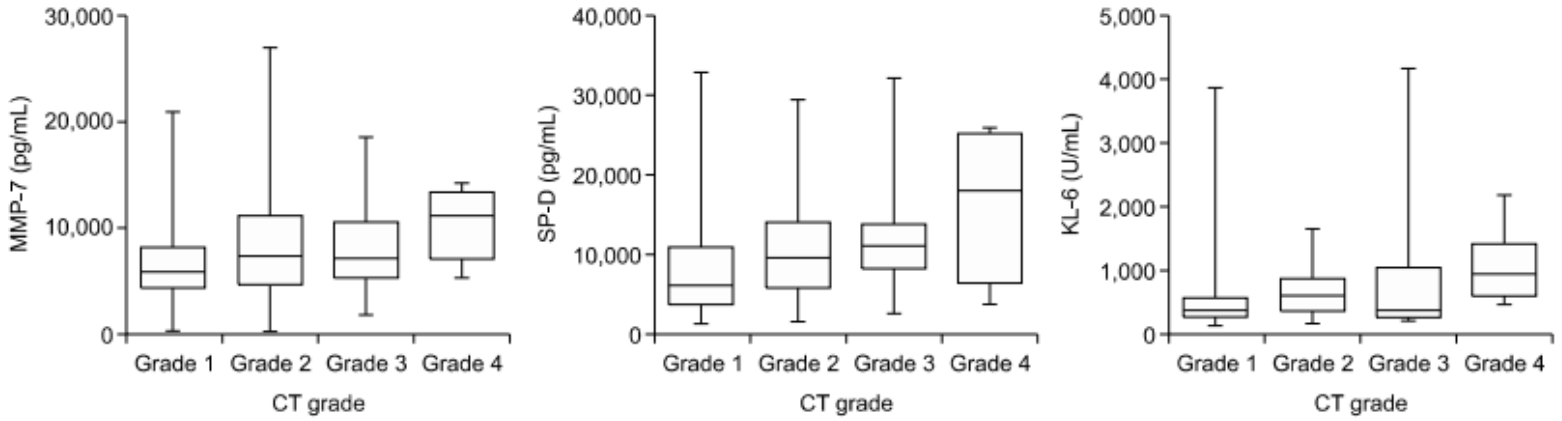


Figure 2. Serum MMP-7, SP-D, and KL-6 levels according to semiquantitative CT grades. MMP-7: matrix metallopeptidase 7, SP-D: surfactant protein D, KL-6: Krebs von den Lungen 6, CT: computed tomography.

Moon JY et al. J Rheum Dis 2021; 28(4): 234-241

Changes of Biomarkers in Progressive Fibrosing CTD- ILD

Phase 3, INBUILD trial

Markers of epithelial injury

KL-6
SP-D
CA-125
CA19-9

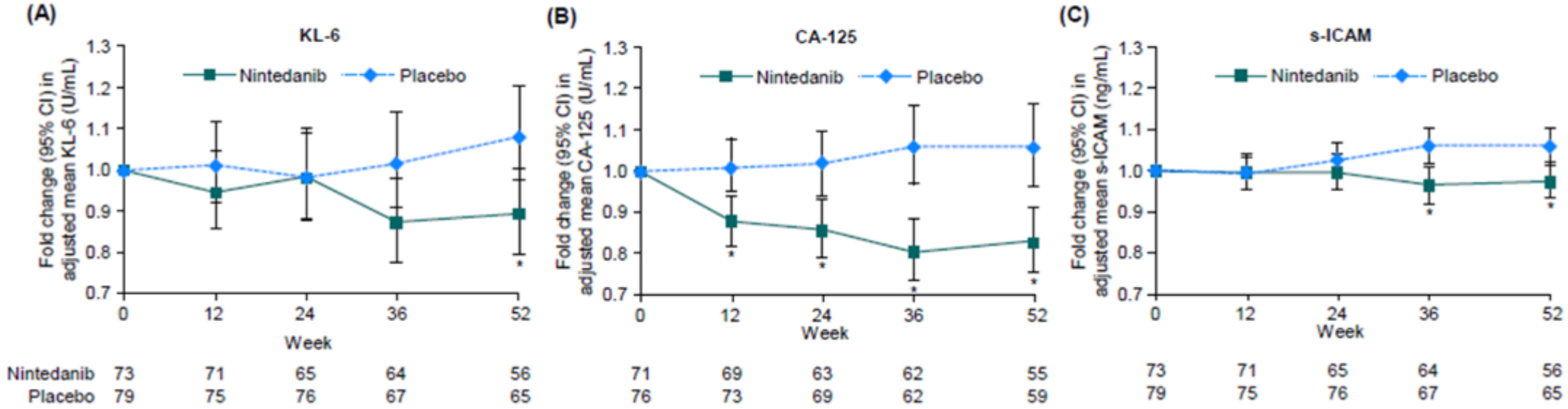
Markers of inflammation

CRP
IL-8
s-ICAM

Markers of ECM turnover

BGM		
C1M	C6M	CRPM
C3M	EL-NE	Pro-C3
C5M	MMP-7	Pro-C6

Figure 2. Changes in circulating levels markers of epithelial injury **(A)** KL-6 and **(B)** CA-125, and inflammation **(C)** s-ICAM, in patients with autoimmune disease-related ILDs in the INBUILD® trial



Maher T et al. Ann Rheum Dis 2023;82(suppl 1):722

Susceptibility Genes : *MUC5B*

JRD Journal of Rheumatic Diseases
Vol. 29, Suppl. 1, May, 2022
KCR 2022
May 19(Thu) - 21(Sat), 2022

O-64

Association analysis of a MUC5B promoter variant rs35705950 with rheumatoid arthritis-interstitial lung disease in Korea

Young Bin Joo[1], So-Young Bang[1,2], Soo-Kyung Cho[2,3], Chan-Bum Choi[2,3], Yoon-Kyoung Sung[2,3], Tae-Hwan Kim[2,3], Jae-Bum Jun[2,3], Dae Hyun Yoo[2,3], Sang-Cheol Bae[2,3], Hye-Soon Lee[1,2]

[1] Division of rheumatology, Department of internal medicine, Hanyang University Guri Hospital, Guri, Republic of Korea
[2] Hanyang University Institute for Rheumatology Research, Seoul, Republic of Korea
[3] Department of rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Republic of Korea

Background

It has been suggested that idiopathic pulmonary fibrosis and rheumatoid arthritis-interstitial lung disease (RA-ILD) share genetic background, among which a MUC5B promoter variant rs35705950 has been reported to be the most significant risk variant for RA-ILD in Caucasian populations. However, this MUC5B variant has shown different genetic traits according to ethnicity. Until recently. little is known about the significant association of MUC5B with RA-ILD in Asian populations. This study aimed to identify the association of MUC5B variant rs35705950 with Korean RA-ILD patients.

Methods

Patients were recruited from Hanyang university hospital for rheumatic diseases (n=1,846). RA-ILD was defined based on chest CT or chest x-ray. The MUC5B variant rs35705950 was genotyped by TaqMan genotyping assays. The chi-square test was used to test for differences in MUC5B variant between RA-ILD and RA without ILD group (RA-noILD).

Results

The minor allele frequency of MUC5B variant was 0.0046. The number of wild-type (GG), heterozygous (GT) and mutant genotype (TT) were 1,829, 17, and 0, respectively. There was no difference of heterozygous between two groups (n=2/75, 2.7% for RA-ILD, n=15/1770, 0.8% for RA-noILD, P=0.150). Among the 350 RA patients who had chest CT, the prevalence of RA-ILD was 16.3% (n=57/350). UIP pattern (45.6%) was the most frequent, followed by nonspecific interstitial pneumonia (22.8%), indeterminate (15.8%) and organizing pneumonia (14.0%). No association was observed in chest CT-confirmed RA-ILD with MUC5B variant (heterozygous number=2/57, 3.5% for RA-ILD, n=8/293, 2.7% for RA-noILD, P=0.669)

Conclusions

Although MUC5B variant is common and strongly associated with RA-ILD in Western population, it is rare in Korean RA patients and appears to be insignificant as a genetic risk factor for Korean RA-ILD patients. These results support the concept that the genetic background of RA-ILD differs according to ethnicity, raising the need to search for novel genetic risk factors for RA-ILD in Korean.

Gain of function Variant in the ***MUC5B***

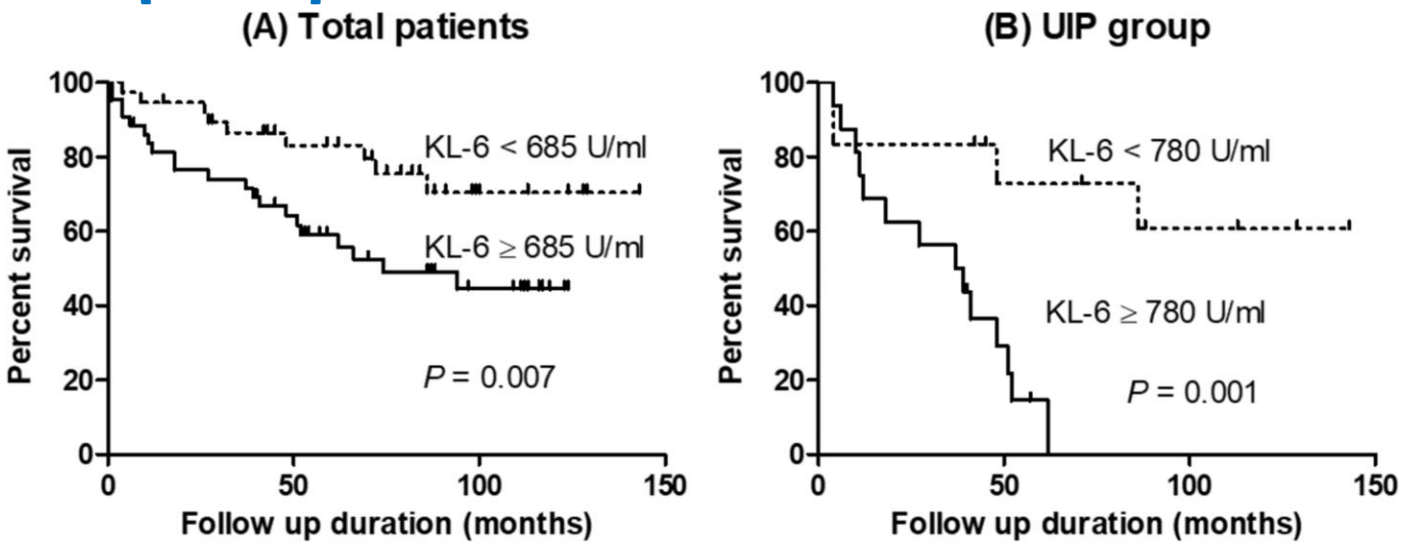
- Strongest genetic risk for IPF, observed in 50% of patients
- Associated with the abnormal production of surfactant protein C secreted from type 2 alveolar epithelial cells
- Tested in 620 RA-ILD, 614 RA without ILD, 5448 unaffected Dominant genotypic association of the *MUC5B* promoter variant rs35705950 with RA-ILD (OR 3.8), and a pattern of UIP on imaging controls.
- whereas it is not associated with systemic sclerosis or myositis-associated ILD.

Juge et al. N Engl J Med 2018; 379:2209-19, Wang D et al. Nat Rev Rheumatol 2019;15:581-96.

KL-6 in RA-ILD

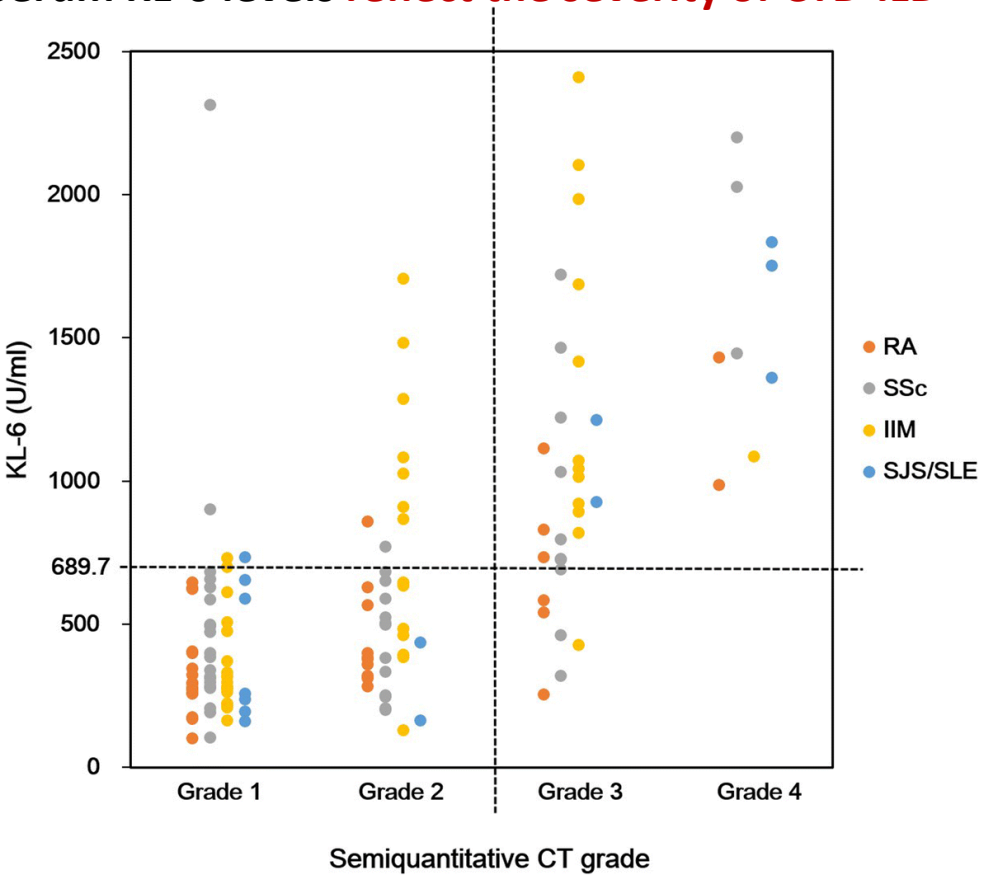
- high KL-6 level (> 640 U/mL) was an independently associated with a UIP pattern and independent prognostic factor for the mortality in RA-ILD

[RA-ILD]



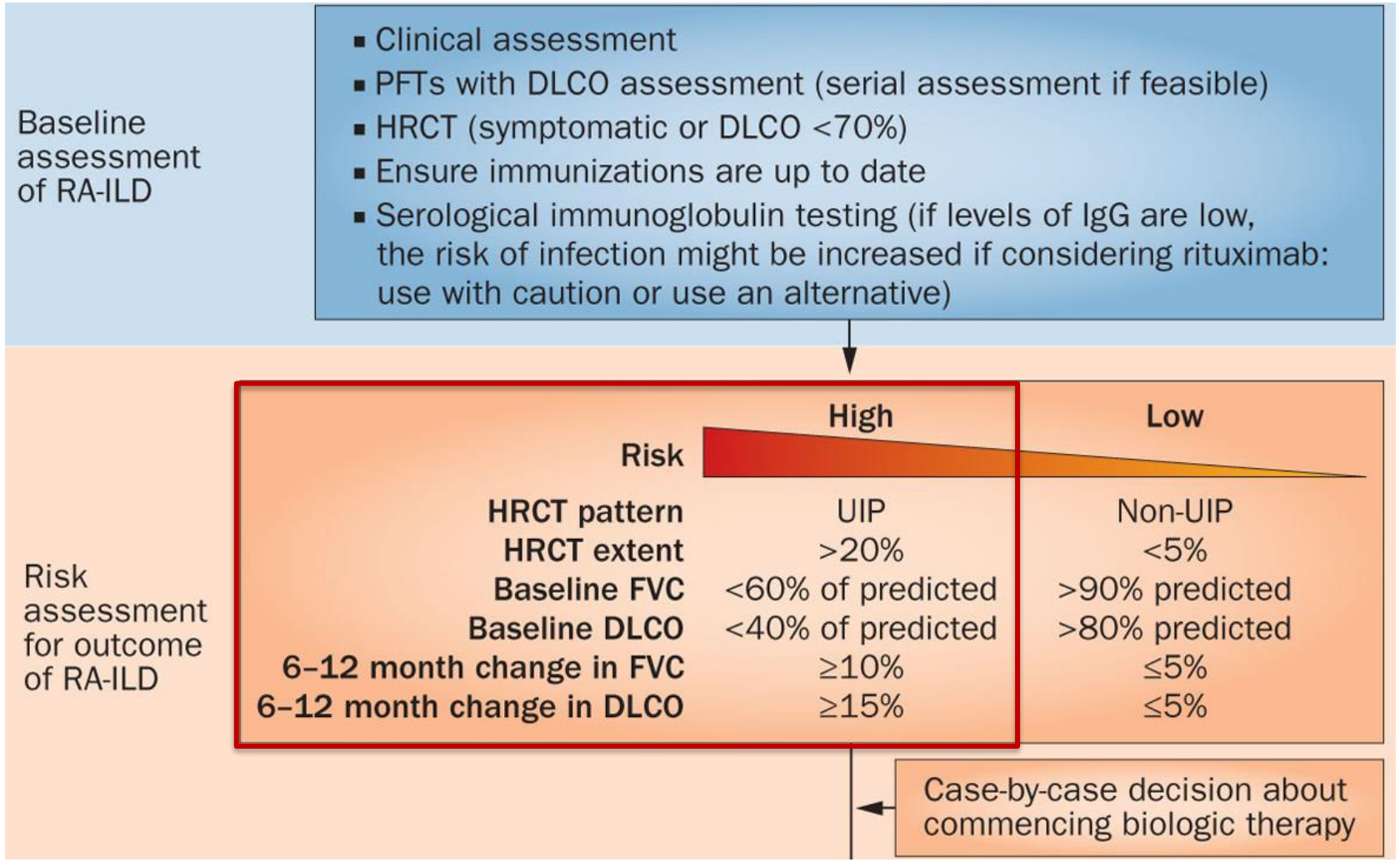
HC Kim et al. PLoS One. 2020; 5(3): e0229997.

- **Serum KL-6 levels reflect the severity of CTD-ILD**



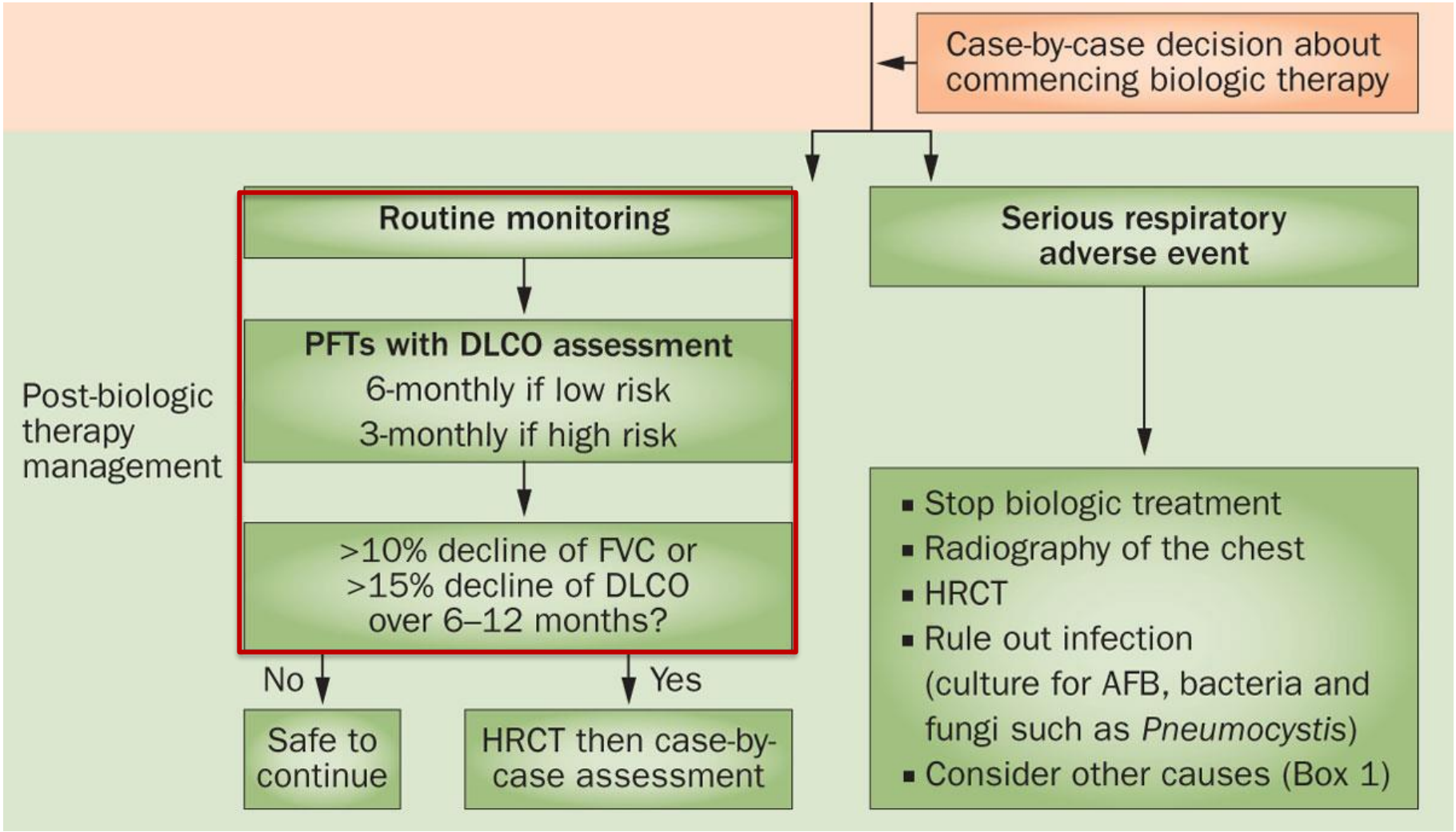
Lee et al. Arthritis Research & Therapy. 2019; 21:58

Suggested Algorithm For Monitoring of RA-ILD on Biologic Tx



Jani M et al. Nat Rev Rheumatol . 2014 May;10(5):284-94

Suggested Algorithm For Management of RA-ILD on Biologic Tx



Jani M et al. Nat Rev Rheumatol . 2014 May;10(5):284-94

Suggested Monitoring of RA-ILD

British Rheumatoid Interstitial Lung (BRILL) Network

RHEUMATOLOGY

Rheumatology 2014;53:1676–1682
doi:10.1093/rheumatology/keu165
Advance Access publication 23 April 2014

Original article

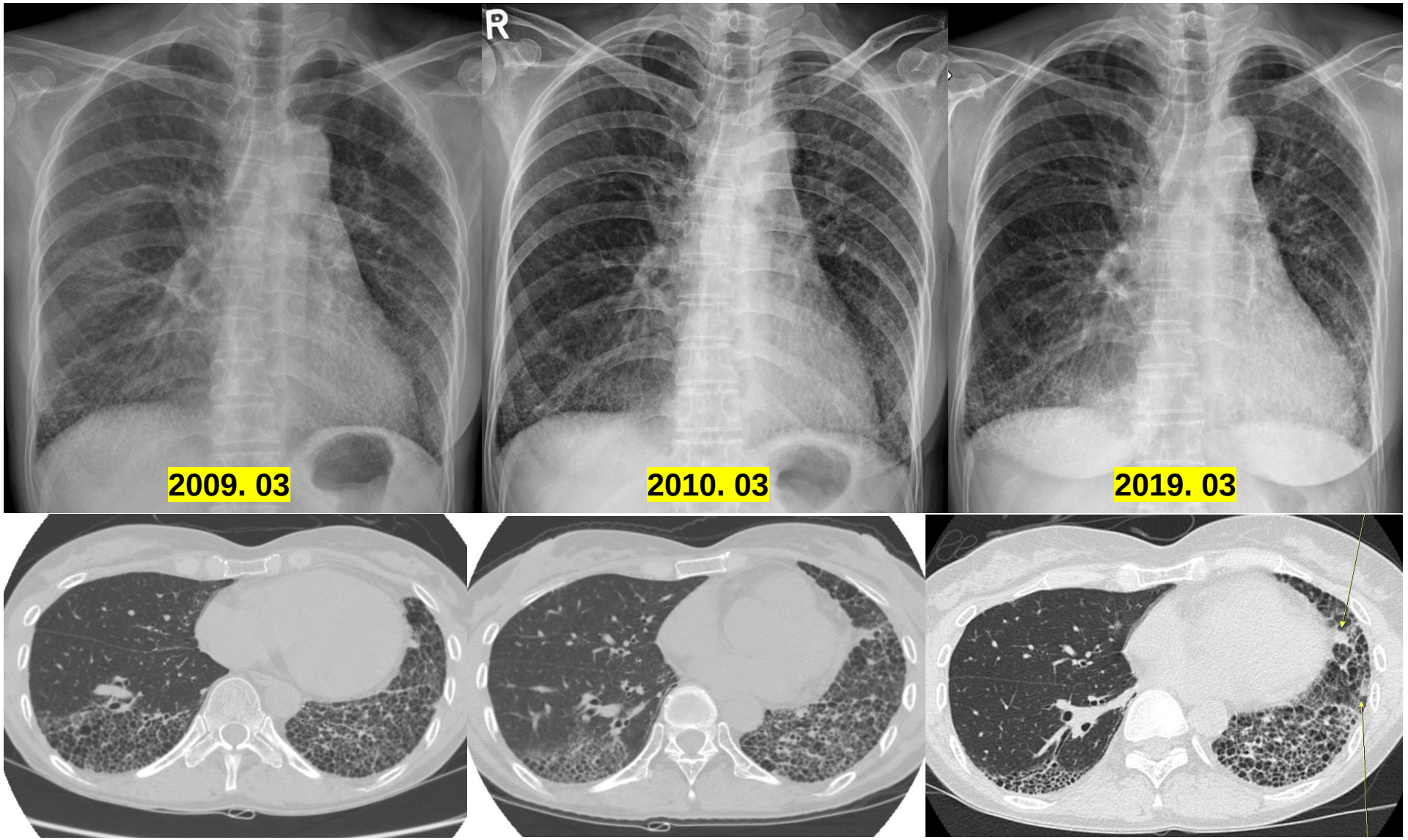
Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics—a large multicentre UK study

- From BRILL1,2 study, PFTs every 6 Months looking for decline in FVC by >10% in one year, HRCT every two years looking for an increase in percentage lung involvement to over 20%
- The presence of UIP and extensive disease are associated with increased mortality.
- Baseline DLco is a useful screening tool for ILD, while the preservation of FVC at baseline might predict limited disease on HRCT.

CA Kelly et al. Rheumatology 2014;53:1676-82

Case . F/55, RA with UIP Clinical course

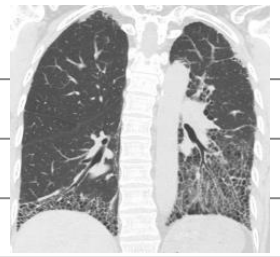
MTX 12.5mg/week + Tacrolimus 2~3mg/day (2009.12~ present)



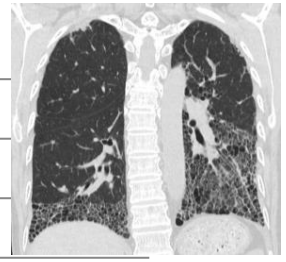
Case . F/55, RA with UIP Clinical course

MTX 12.5mg/week + Tacrolimus 2~3mg/day (2009.12~ present)

Absolute change from baseline in FVC (mL)



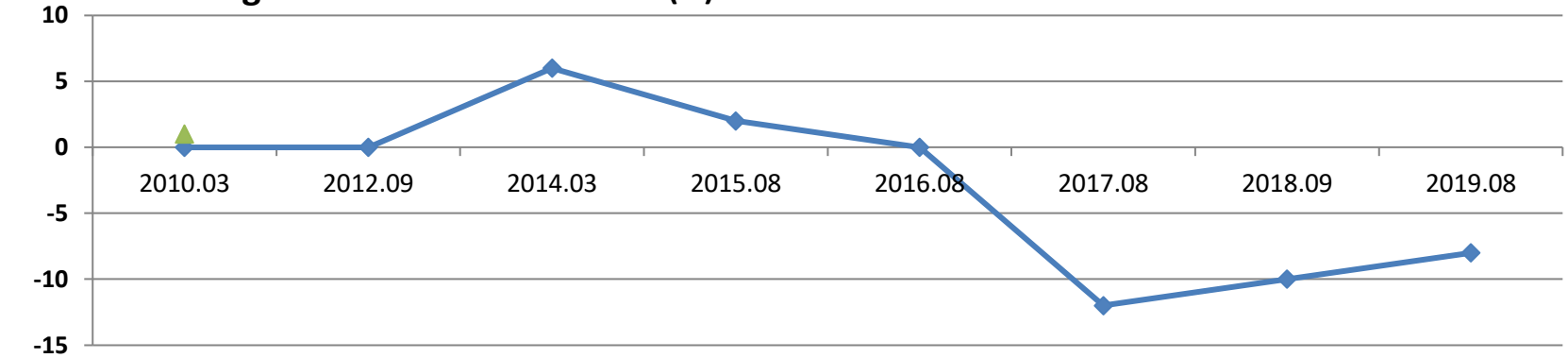
2017.06



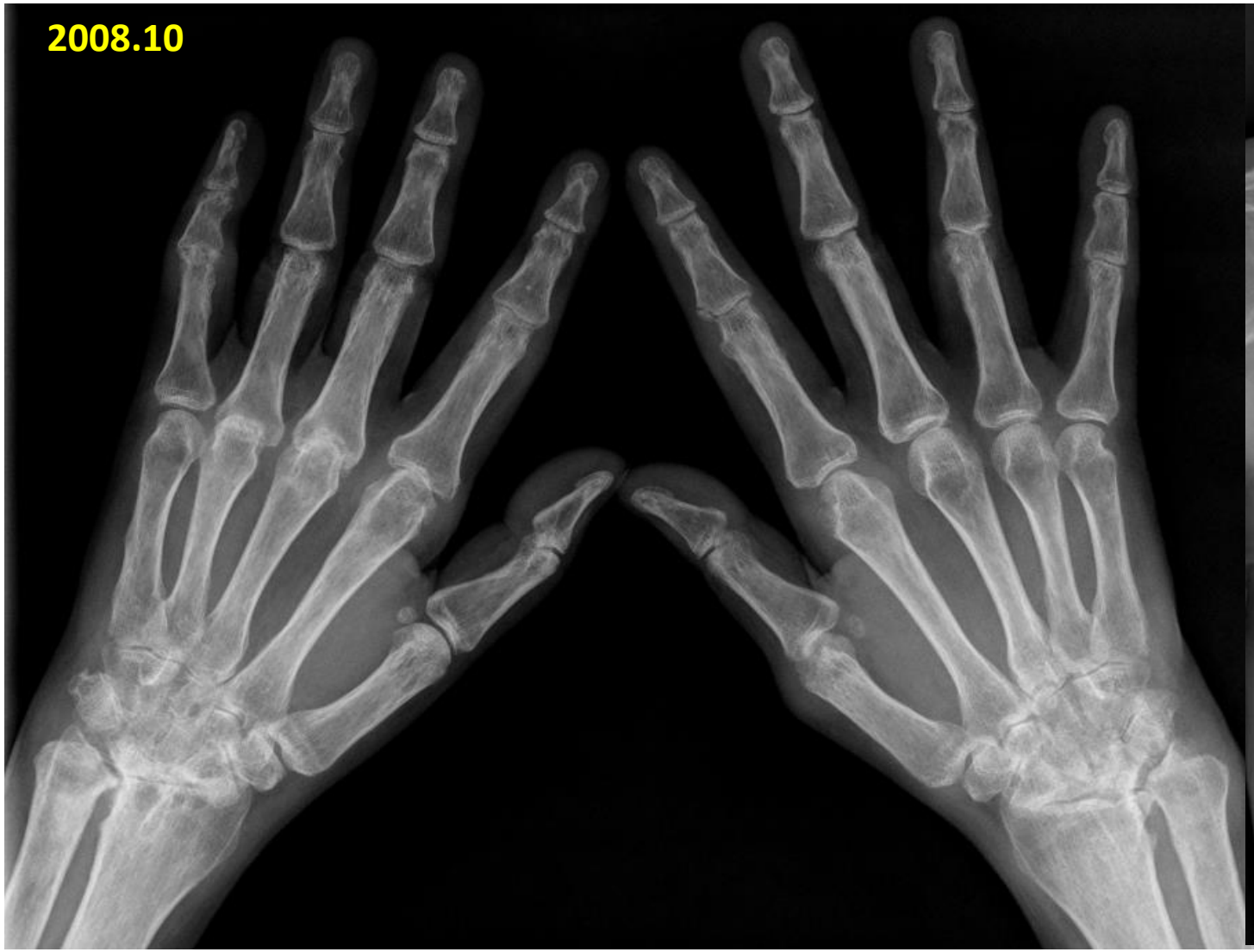
2019.11

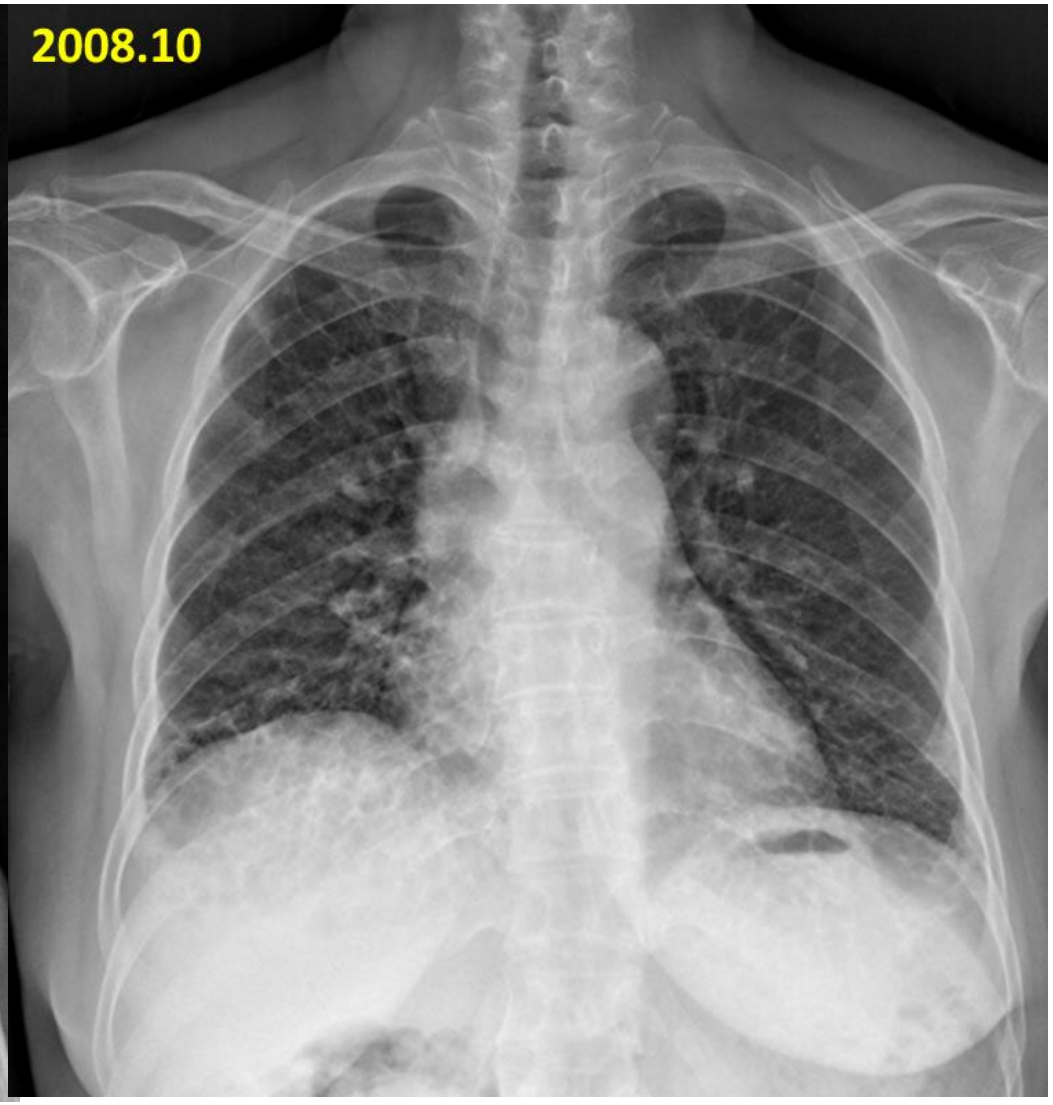
MTX 15mg/week + Tacrolimus 2-3mg/day (2009.12~ Present)

Absolute change from baseline in DLco (%)

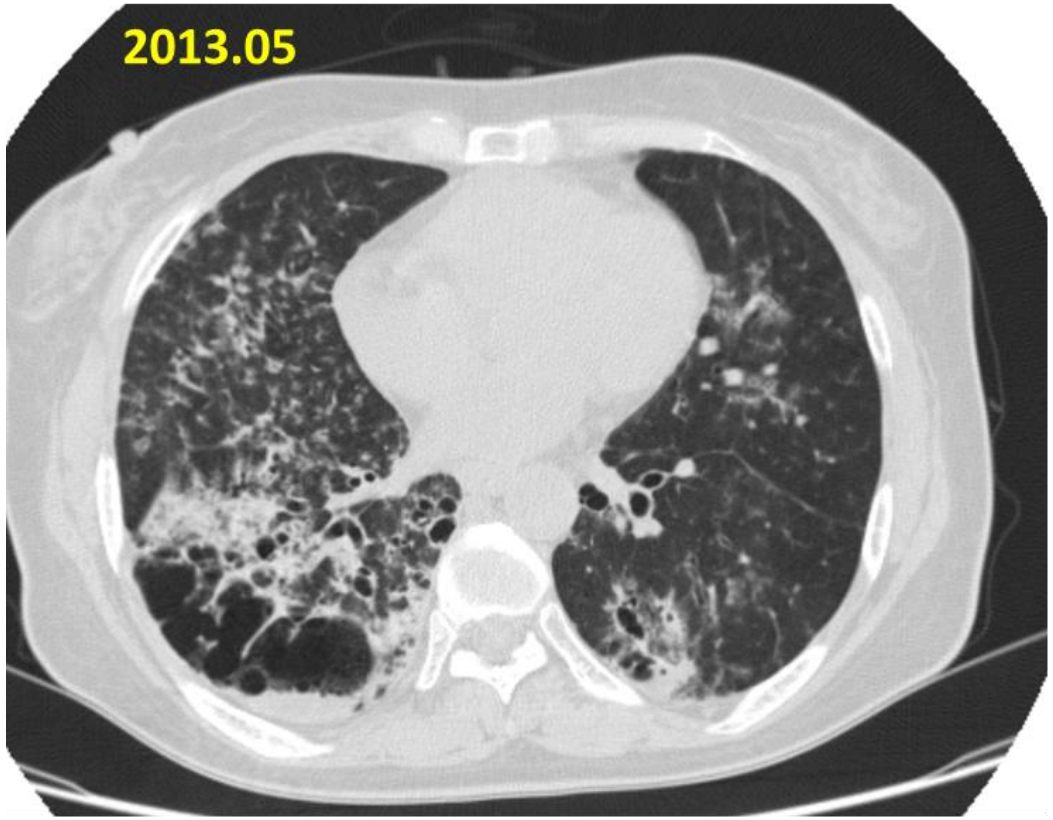


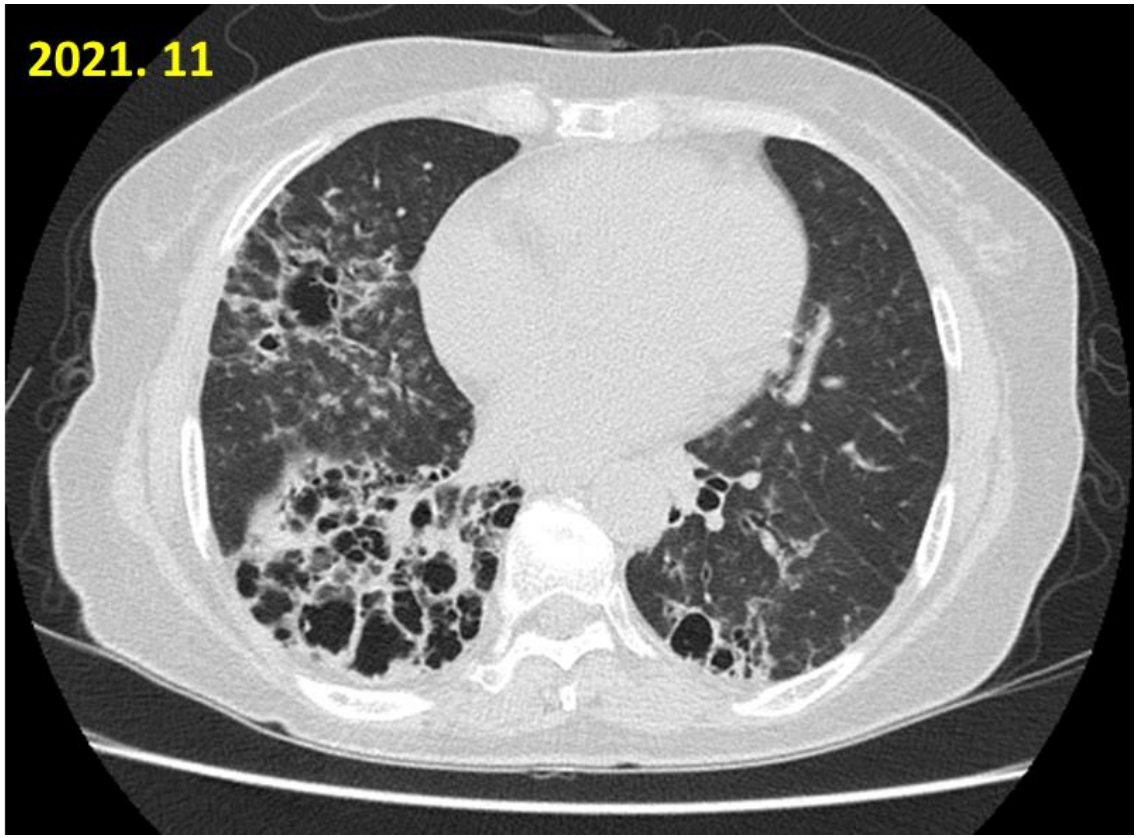
Case . F/52 SPRA with UIP





Case . SPRA with UIP





honeycomb cysts, reticulation, traction bronchiectasis

MTX+ TAC (2013.05~2015.03) → Abatacept+ TAC (2015.10~현재)

Case . Pulmonary Function Change: 2013.05~Present

- 폐기능검사

% of predicted value / date	2013.05	2014.05	2016.01	2018.06	2020.06	2021.09
FVC	82	78	68	68	71	68
FEV1	94	84	74	72	80	76
FEF_{25-75}	95	124	80	83	68	98
DLco	66	51	48	51	51	54

- 6분 도보검사

	2013.05	2014.05	2016.01	2018.06	2020.06	2021.09
최소 SpO2	92%	91%	93%	91%	93%	93%
6분간 걸은 거리	361 m	456m	479m	488m	447m	420m

MTX+ TAC (2013.05~2015.03) → Abatacept+ TAC (2015.10~현재)

- TTE (20.06) - TRpv 2.3 m/s, RVSP 26.2 mmHg, NT-proBNP 87.56

Therapeutic Considerations of CTD-ILD

- Re-evaluation of MTX-induced lung injury
- Effect of conventional DMARDs
- Biologics

Studies in 2020 on MTX Use and ILD

Study	Study design	Patients (patient number)	Primary findings
Juge et al.[1]	Retrospective: case-control with validation cohort	Patients with RA-ILD ($n=410$) or with RA without ILD ($n=673$)	Methorexate use was associated with a reduced prevalence and delayed onset of RA-ILD
Robles-Pérez et al.[5]	Prospective cohort	Patients with RA ($n=40$)	Methotrexate use was not associated with the onset or progression of ILD
Ibfelt et al.[6]	Retrospective cohort (Danish national registry)	Patients with RA ($n=30,512$)	Methotrexate use was not associated with an increased risk of ILD
Li et al.[7]	Retrospective cohort	Patients with RA without ILD at diagnosis ($n=923$)	Methotrexate use was not associated with the onset or progression of ILD

→ *MTX delayed the development and slow the progression of ILD*

AU Wells . Nat Rev Rheumatol. 2021;17(2):79-80.

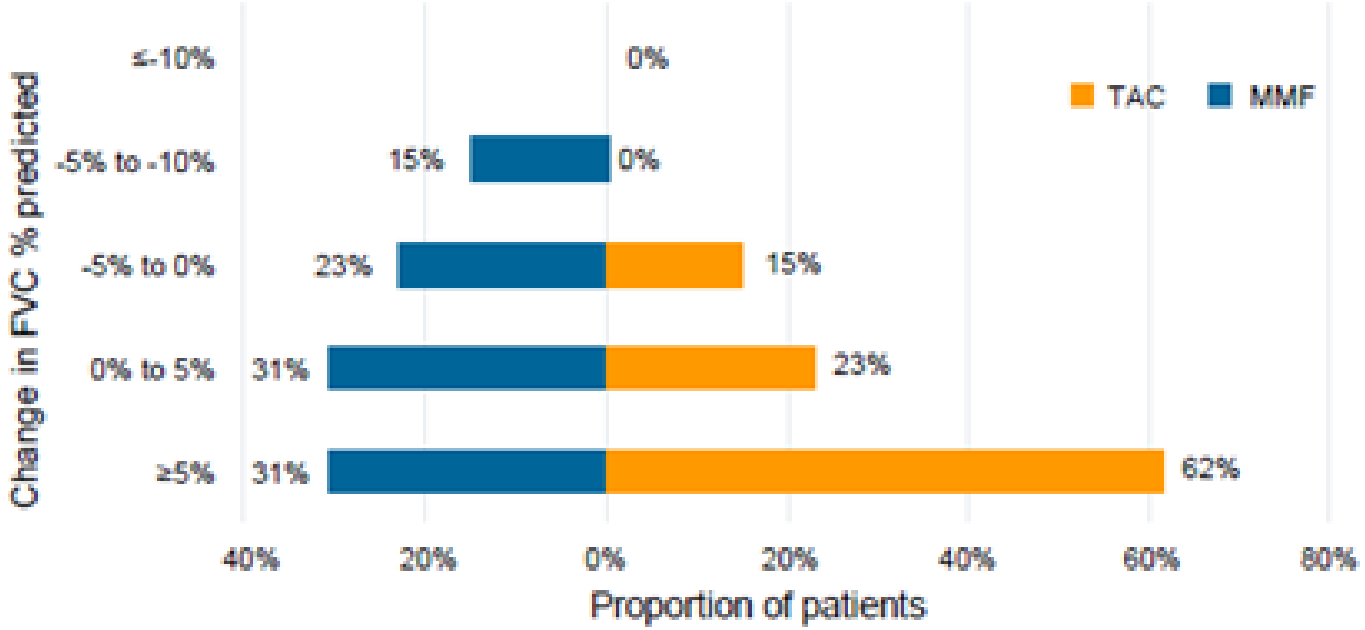
MMF vs TAC in Patients with SSc-ILD

INSIST trial : Single center RCT

Table 1. Change in FVC % predicted over 24 weeks in patients with SSc-ILD receiving MMF or TAC

	MMF (n=13)	TAC (n=13)	Difference (95% CI)	*P* value
FVC % pred. mean±SD	+4.4±10.6	+6.9±8.4	2.52% (-10.3–5.2)	0.500

Figure 1. Stratified change in FVC% predicted over 24 weeks in patients with SSc-ILD receiving MMF or TAC



Figures from Mathew J et al. Ann Rheum Dis 2023;82(suppl 1):160. © 2023 BMJ Publishing Group Ltd. & European League Against Rheumatism. Reproduced with permission from BMJ Publishing Group Ltd.

Mathew J et al. EULAR OP0240

Biologics for RA Patients with ILD

GUIPCAR 2017

Guidelines for the management of RA in Spain

In patients with RA, which is the safest biological treatment in patients who also have ILD?

Recommendation and degree of recommendation after systematic review of the literature

- In patients with RA and ILD who require biological therapy, it is recommended to use **ABA** as the safest option (Recommendation grade C)

  As an alternative, **RTX** can be used (Recommendation grade D)

Sociedad Española de Reumatología

The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis 2019

Respiratory disease

British Society for Rheumatology

(i) Pre-existing ILD is not a specific contraindication to biologic therapy; however, caution is advised in patients with poor respiratory reserve (in whom a significant drop in lung function would be potentially life threatening); in this situation it is advised to work closely with a respiratory physician with a specialist interest in ILD (grade 2C, SOA 99%).

(ii) RTX or ABA may be considered a first-line biologic in patients with ILD (grade 2C, SOA 84%)

2022 Taiwan Consensus Recommendation

Consensus recommendations on the management of selected comorbidities in rheumatoid arthritis (RA) in Taiwan.

Recommendations	SoR	QoE	Agreement (%)
1. The assessment of CVD risk is recommended in adult patients at the diagnosis of RA, at least once every 5 years, and at the time of major changes in DMARDs therapy.	A	C	100
2. CVD risk assessment using QRISK2 is recommended for RA patients.	B	D	93.3
3. The management for RA patients with hypertension or dyslipidemia should be carried out according to national guidelines as for diabetes mellitus patients.	A	C	100
4. Adequate control of RA activity is recommended for all patients; if in low disease activity, use the lowest possible dose of corticosteroids and prescribe NSAIDs with caution.	A	B	100
5. Osteoporosis (OP)/fragility fracture risk assessment is recommended for RA patients, including clinical risk factors, DXA, FRAX and falls risk, at least once every 3 years.	A	C	100
6. A FRAX-based approach with intervention thresholds may be a useful strategy for the treatment of OP and glucocorticoids-induced OP.	A	D	93.3
7. Optimal management of RA patients with OP includes "treat to target" strategy for disease control and anti-osteoporotic medications.	A	C	100
8. ILD risk should be assessed, including risk factors, HRCT and PFTs in RA patients with persistent cough, unexplained dyspnea and/or abnormal CXR.	A	D	100
9. Assessment of pattern/extent of ILD using multidisciplinary decision (MDD) among rheumatologists, radiologists, and pulmonologists is recommended for RA-ILD patients.	A	C	100
10. The use of MTX or leflunomide should be avoided in RA patients with moderate/severe ILD. Rituximab or abatacept may be the first-line biologic in RA-ILD patients with limited evidence.	B	D	86.7
11. Treatment of moderate/severe RA-ILD should be individualized based on HRCT pattern/extent. Corticosteroids are the mainstay of management, and mycophenolate or cyclophosphamide may be effective but adverse effects should be monitored.	A	D	93.3

Yu et al. Medicine (Baltimore). 2022;101(1):e28501

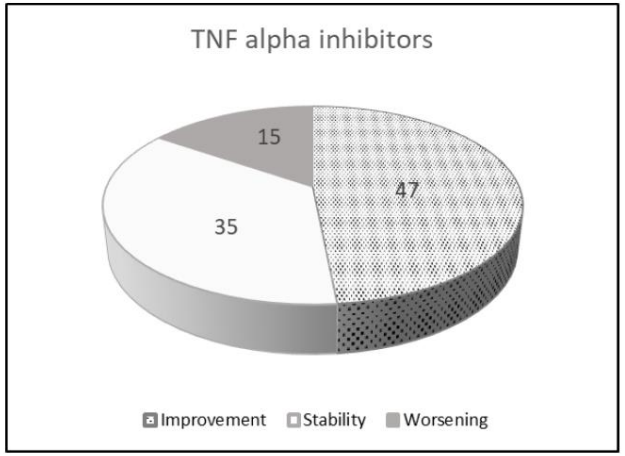
Impact of TNF-Inhibitors on RA-ILD

- TNFi has been associated by many Authors to new onset or exacerbation of RA-ILD
- Other studies confused lung toxicity for TNFi and showed that these drugs can stabilize or even improve pulmonary interstitial disease

J. Clin. Med. 2020, 9, 1082

TNF Alpha Inhibitors		
		Number of patients 96
Improvement	47	48.4%
Stability	35	36.1%
Worsening	15	15.5%
Author, year (Ref)	Article type	
Schultz R, 2001 [118]	case report	1
Vassallo R, 2002 [107]	case report	1
Bargagli E, 2004 [111]	case report	1
Antoniou KM, 2007 [112]	prospective case series	3
Wang Y, 2011 [119]	case report	1
Komiya K, 2011 [114]	case report	1
Nakashita T, 2014 [109]	retrospective review	46
Detorakis EE, 2017 [108]	prospective study	42
Other articles *		
Kurata I, 2019 [131]	retrospective study	30

Cumulative data on more diseases or drugs. Patients not included for the evaluation of lung outcome.



Pulmonary effects of TNFi in RA-ILD patients: a review of the literature.

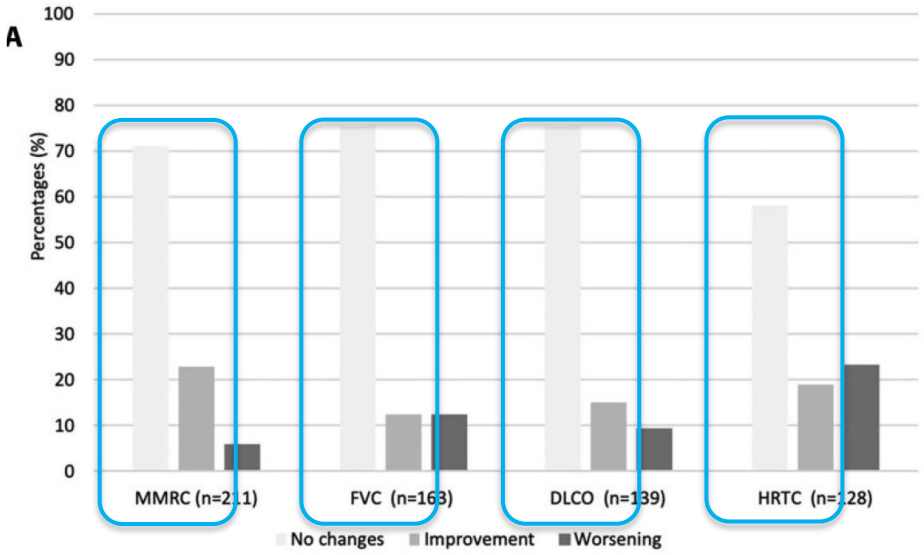
- Recently, the NICE and Spanish Society of Rheumatology contraindicated TNFi in this population

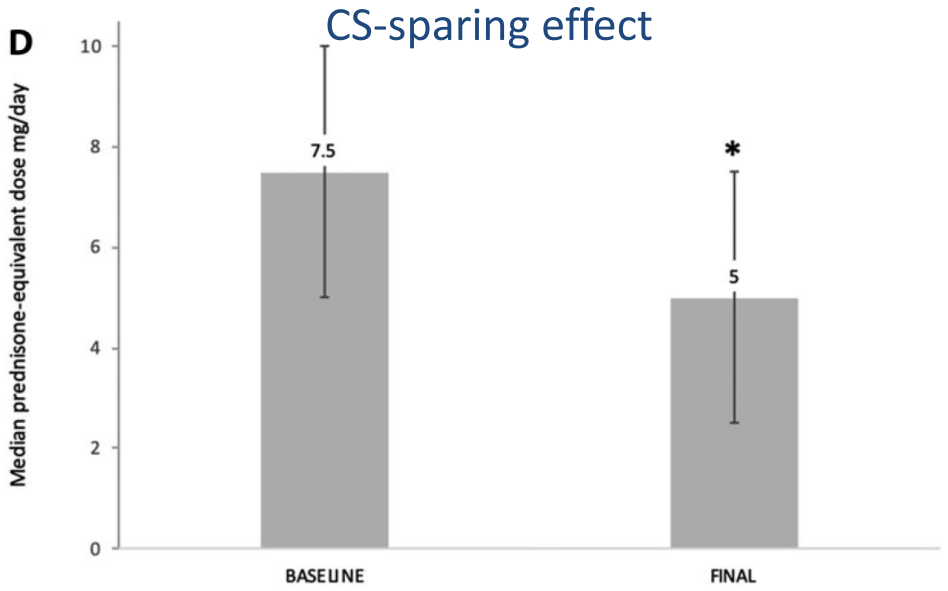
Rheumatology (Oxford) 2019, 58, e3–e42.

Abatacept in RA-ILD

National Multicenter, Open-Label Registry in Spain

- 263 RA-ILD patients (150 women) with RA-ILD undergoing ABT therapy
- Median follow-up was 12 (6–36) months
- Did not show worsening: dyspnea(MMRC) (91.9%); FVC (87.7%); DLCO (90.6%); and chest HRCT (76.6%).
- CS-sparing effect from a median 7.5 to 5mg/day at the end of follow-up (P<0.001)





C Fernández-Díaz et al. Rheumatology 2020;0:1–11

Tocilizumab Tx for RA-ILD

Retrospective, National Multicenter Study in Italy

- Retrospectively collected 28 patients with RA-ILD treated with TCZ ≥ 6Mo
- Variation of 10% of FVC or DLCO compared to baseline was considered clinically significant

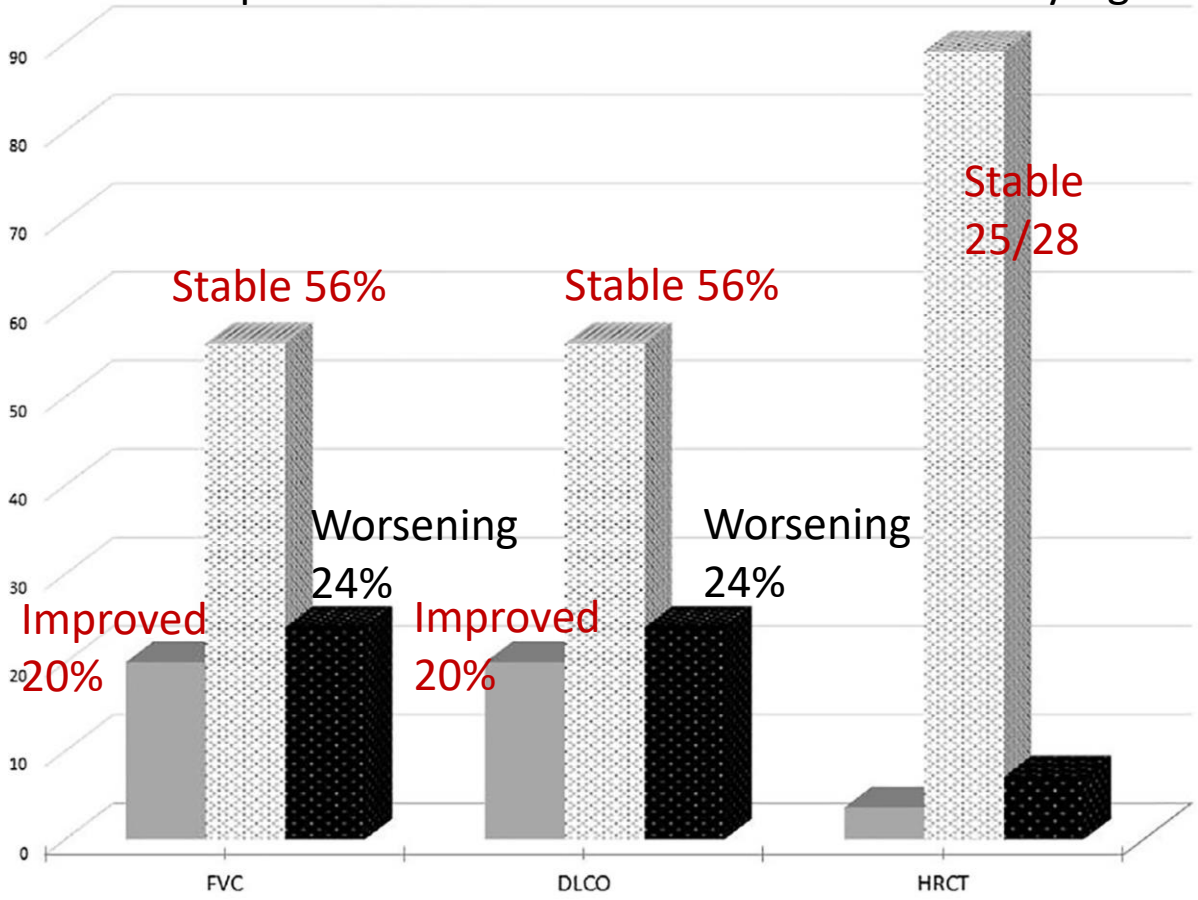
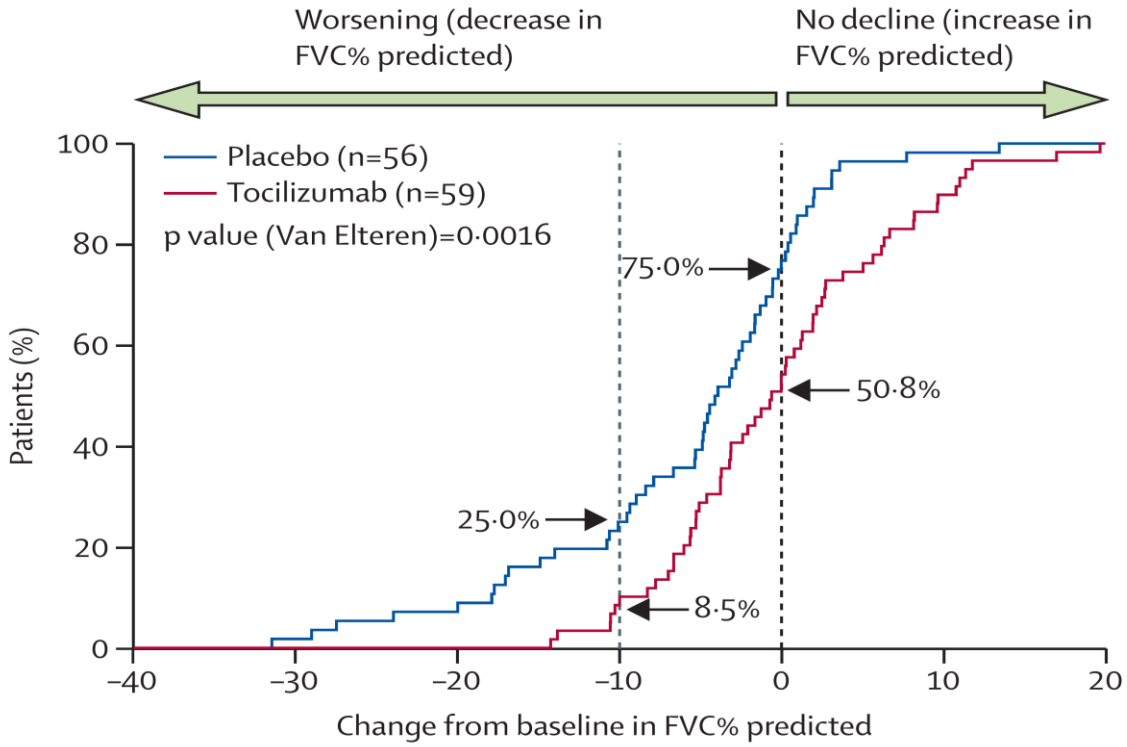


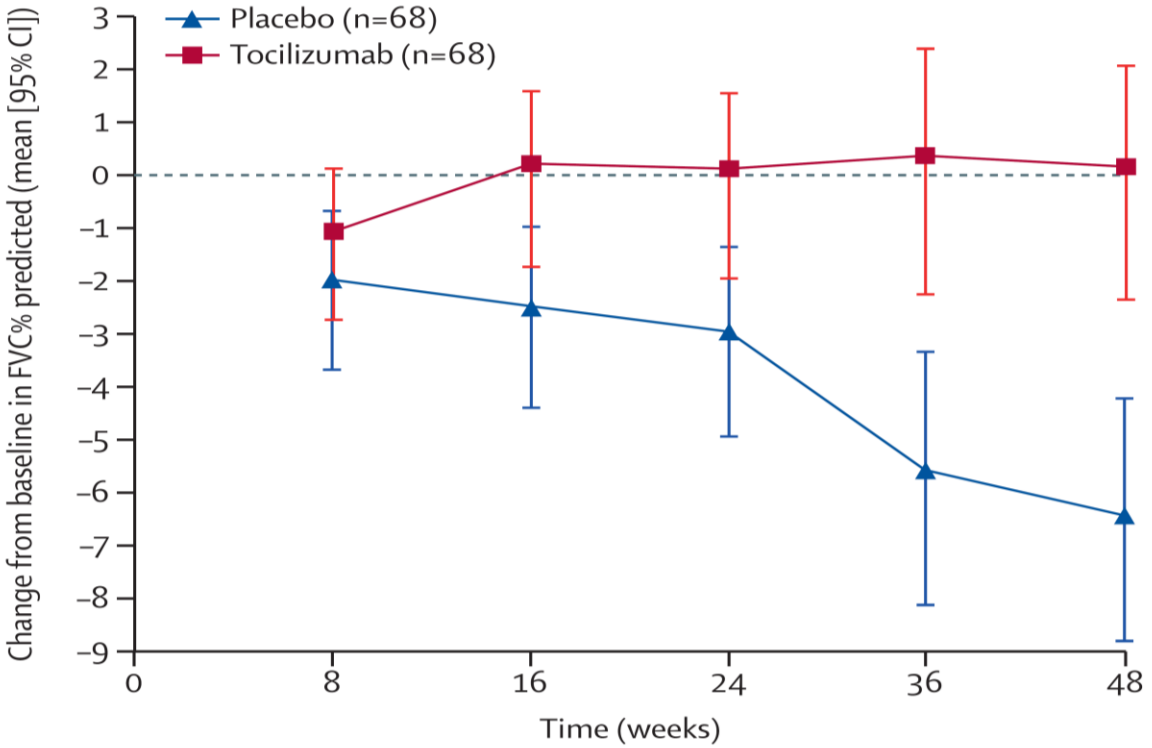
Figure 1 Evolution of lung function and radiology during follow up. (▨), Improvement; (▩), stability; (■), worsening. DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography.

Internal Medicine Journal 50 2020; 50: 1085–90

Tocilizumab Stabilize Lung Function in SSc-ILD

Phase 3, focuSSced Trial





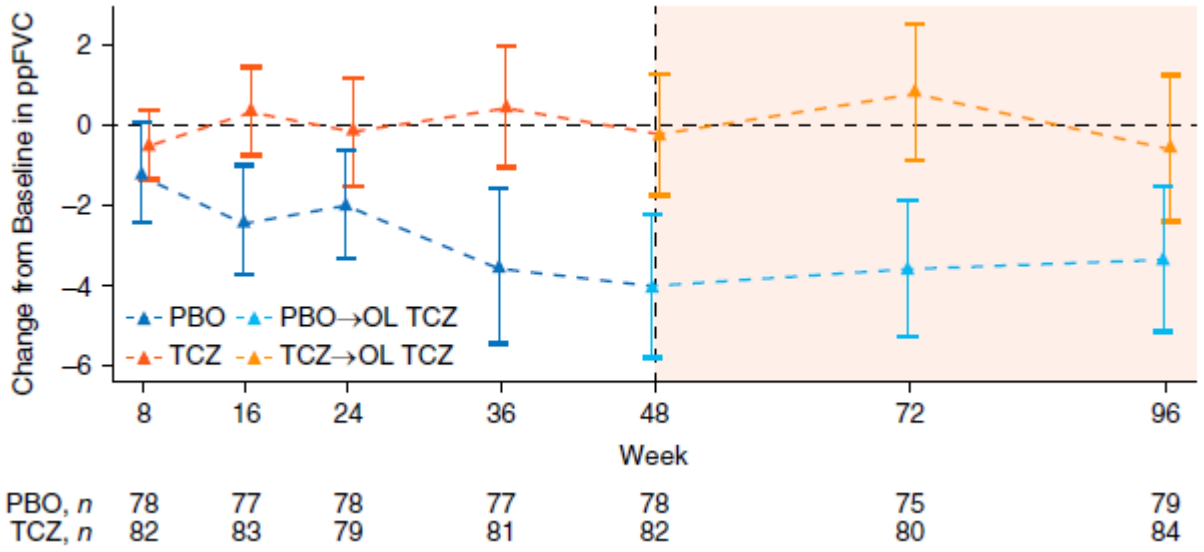
Khanna D et al. Lancet Respir Med 2020;8: 963–74

Long-Term Safety and Efficacy of TCZ in Early SSc-ILD

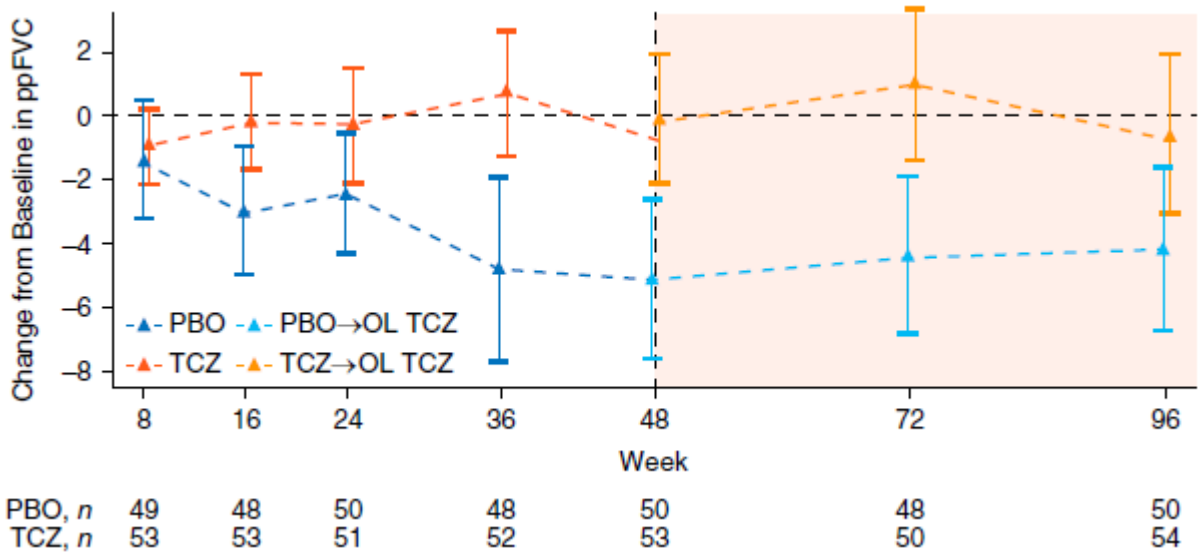
Phase 3 OLE, focuSSced Trial

- Percent predicted FVC mean change from baseline to Week 96

- **All patients**



- **Patients with SSc-ILD at baseline**



Am J Respir Crit Care Med. 2022;205(6):674-684

RTX vs CYC for the CTD-ILD

RECITAL (Phase 2b)

- RTX (1000 mg at weeks 0 and 2 IV) or CYC (600 mg/m² BSA every 4 weeks IV for six doses).
- Primary endpoint : change from baselinein FVC at 24 weeks, using a mixed-effects model with random intercepts, adjusted for baseline FVC and CTD type

Secondary endpoints At 24 weeks	Cyclophosphamide (change from baseline)	Rituximab (change from baseline)	Difference (mixed effects model)	95% confidence interval
FVC (mL)	99 ± 329	97 ± 234	-40	-153 - 74
Dlco (%)	1.43 ± 23.05	6.98 ± 17.19	0.186	-0.054 - 0.425
6 Min Walk Distance (m)	10.4 ± 78.6	10.9 ± 74.2	-0.72	-24.76 – 23.32
SGRQ	-4.8 ± 19.6	-3.4 ± 15.4	0.63	-5.64 – 6.91
K-BILD	9.4 ± 20.8	8.8 ± 17.0	0.40	-5.73 – 6.52
GDAS	-2.9 ± 2.5	-2.8 ± 1.8	-0.14	- 0.85 – 0.57

Time (weeks)

- RTX was not superior to CYC to treat patients with CTD-ILD
- RTX was associated with fewer adverse events→ RTX should be considered as a therapeutic alternative to CYC in individuals with CTD-ILD requiring intravenous therapy.

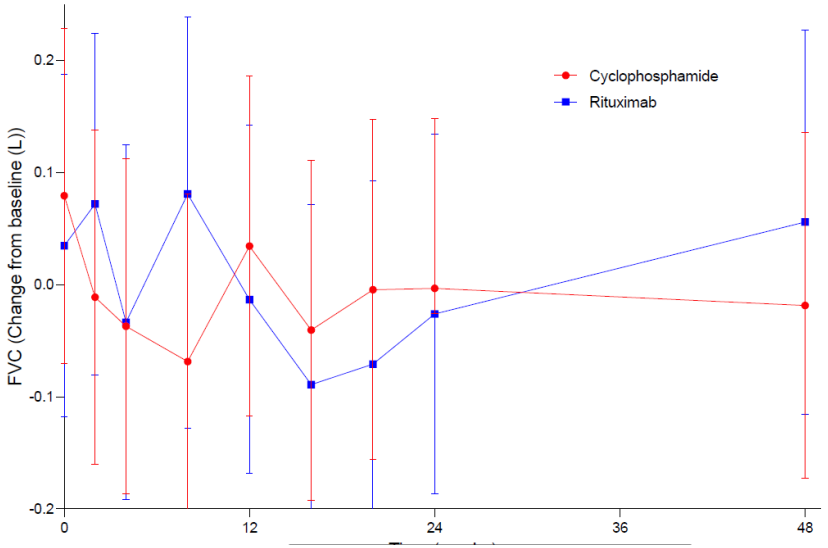
Toby M Maher et al. Lancet Respir Med . 2022 Nov 11 online ahead of print

RTX vs CYC for the CTD-ILD

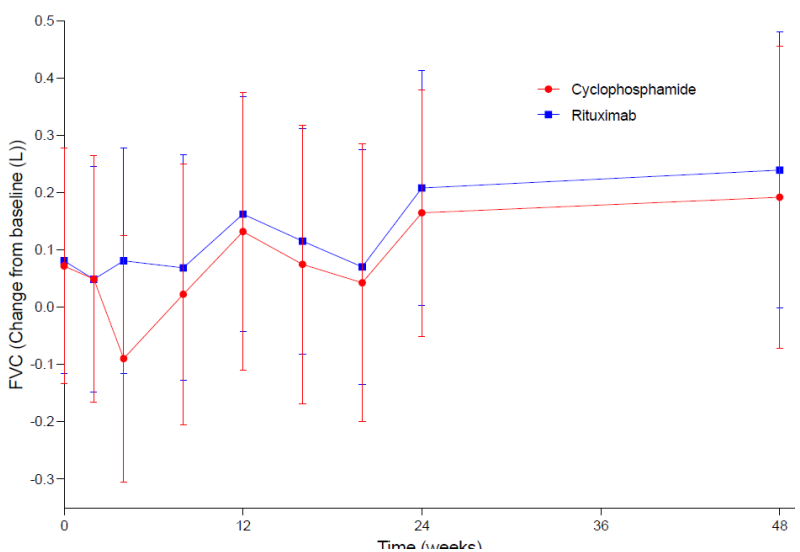
RECITAL (Phase 2b) Subgroup Analysis

- FVC change according to CTD subtypes

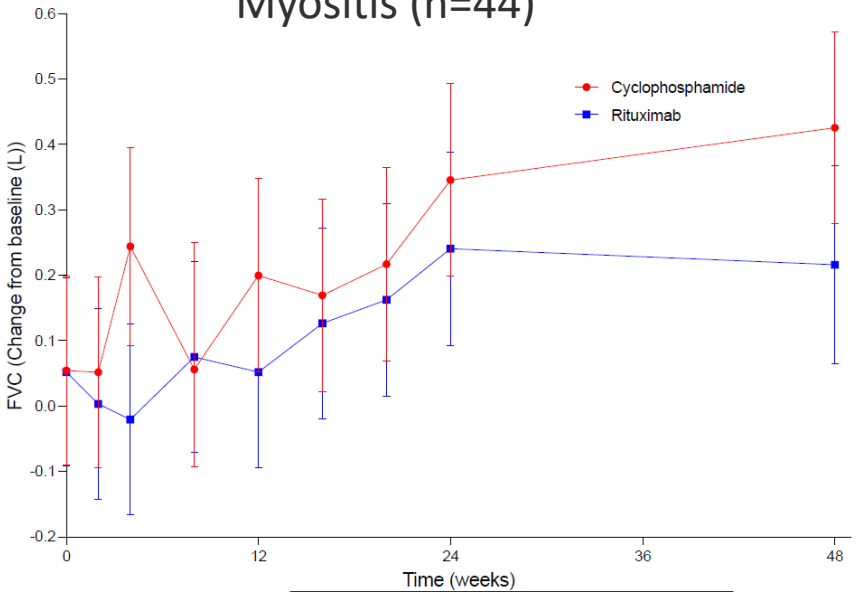
Systemic sclerosis (n=37)



MCTD (n=16)



Myositis (n=44)



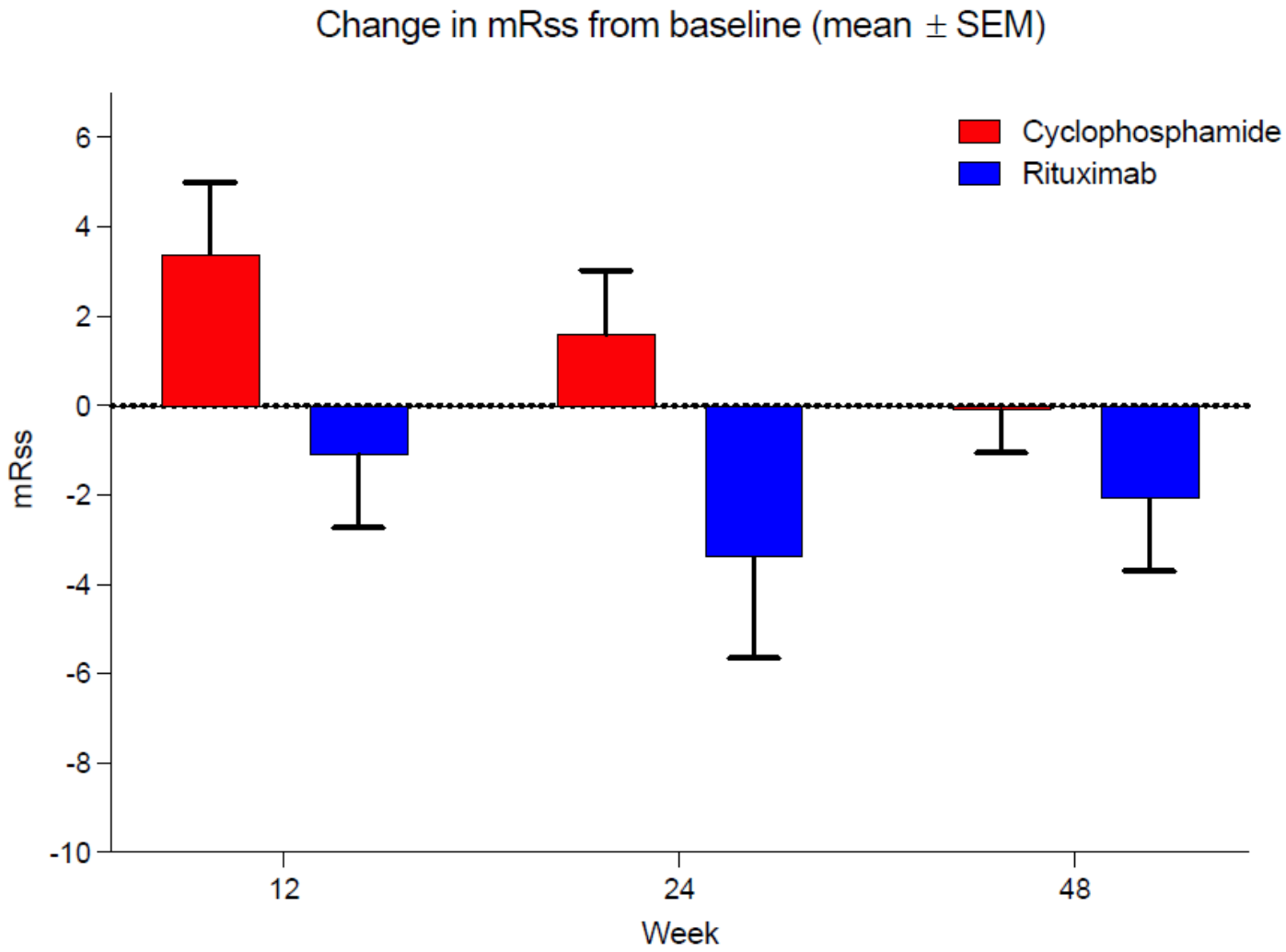
- Both RTX and CYC improve FVC and QoL at 24 and 48 weeks in patients with CTD-ILD
  - No significant difference seen between treatment arms.
  - For SSc-ILD both drugs appear to stabilize FVC over 48 weeks
  - CYC and RTX both resulted in FVC improvements in MCTD and myositis patients

Toby M Maher et al. ACR Convergence 2022

RTX vs CYC for the CTD-ILD

RECITAL (Phase 2b) Subgroup Analysis-

- mRSS Skin Score Change of Scleroderma



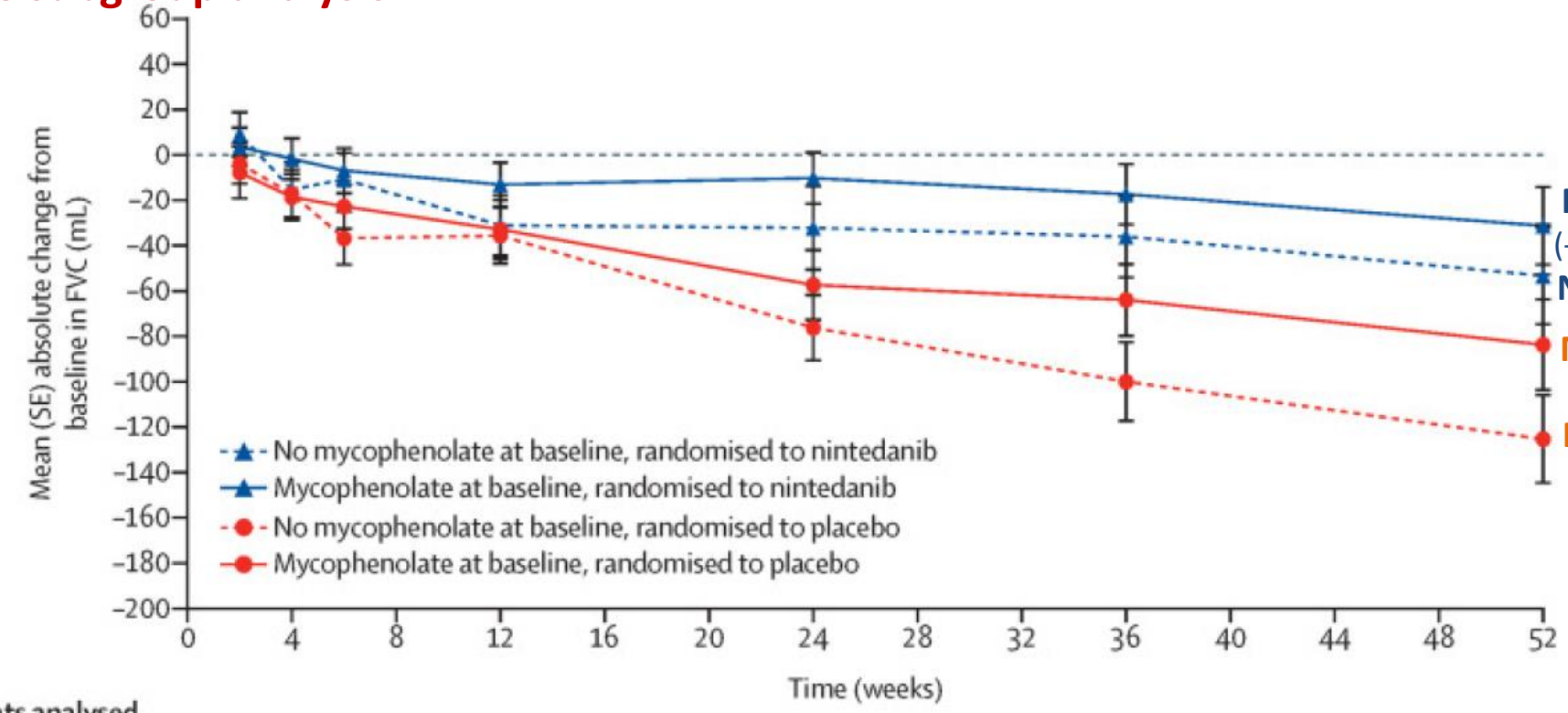
- RTX, but not CYC , improved mRSS in SSc subjects.
- RTX should be considered as an alternative to CYC in individuals with CTD-ILD.

Toby M Maher et al. ACR Convergence 2022

Nintedanib for SSc-ILD

Phase 3, SENCIS trial

- **Mycophenolate subgroup analysis**

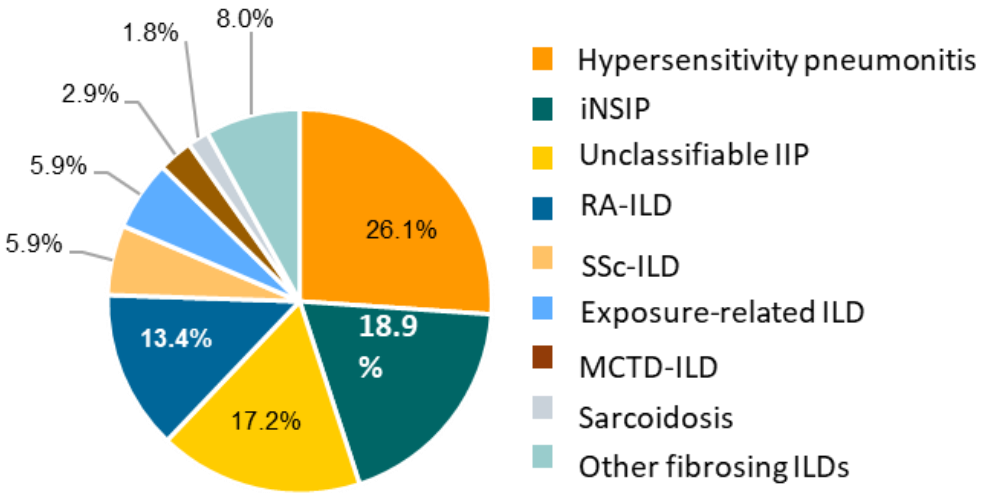


Number of participants analysed					
Nintedanib group, mycophenolate at baseline	138 134 131	135	129	128	116
Nintedanib group, no mycophenolate at baseline	145 147 142	143	136	134	125
Placebo group, mycophenolate at baseline	136 139 139	139	137	133	127
Placebo group, no mycophenolate at baseline	147 142 141	144	143	135	130

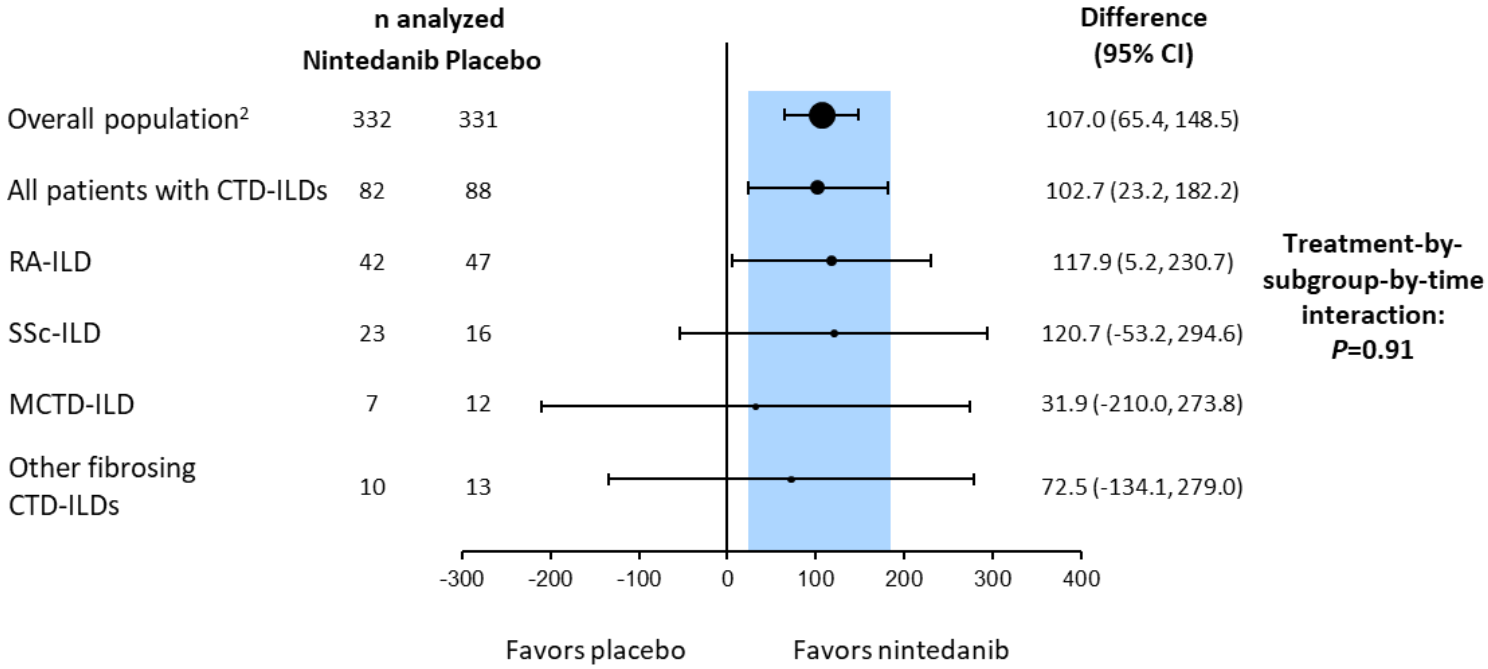
Highland KB et al. Lancet Resp Med 2021; 8:90196.

Effect of Nintedanib on Slowing FVC Decline : Consistent Across Subgroups (Phase 3, INBUILD trial)

- ~25% of overall INBUILD population were patients with CTD-ILDs



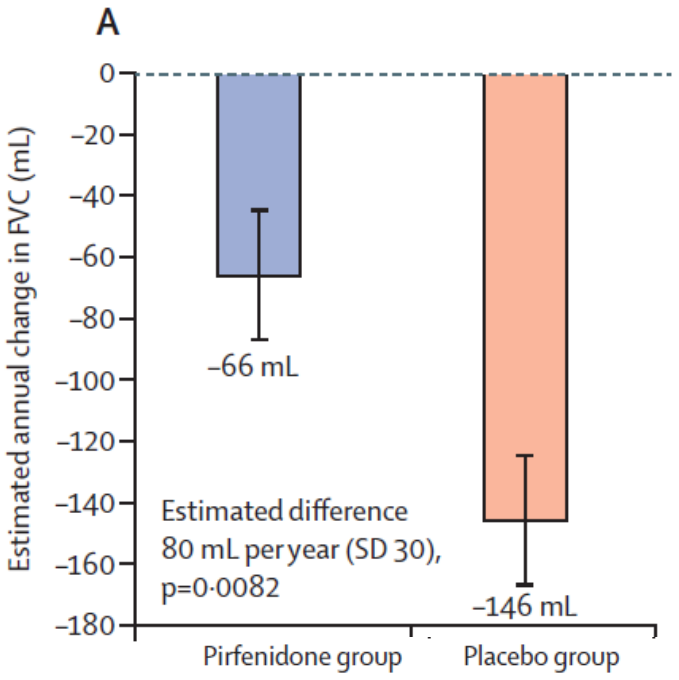
- Annual rate of decline in FVC (mL/year) over 52 weeks in patients with CTD-ILDs in INBUILD

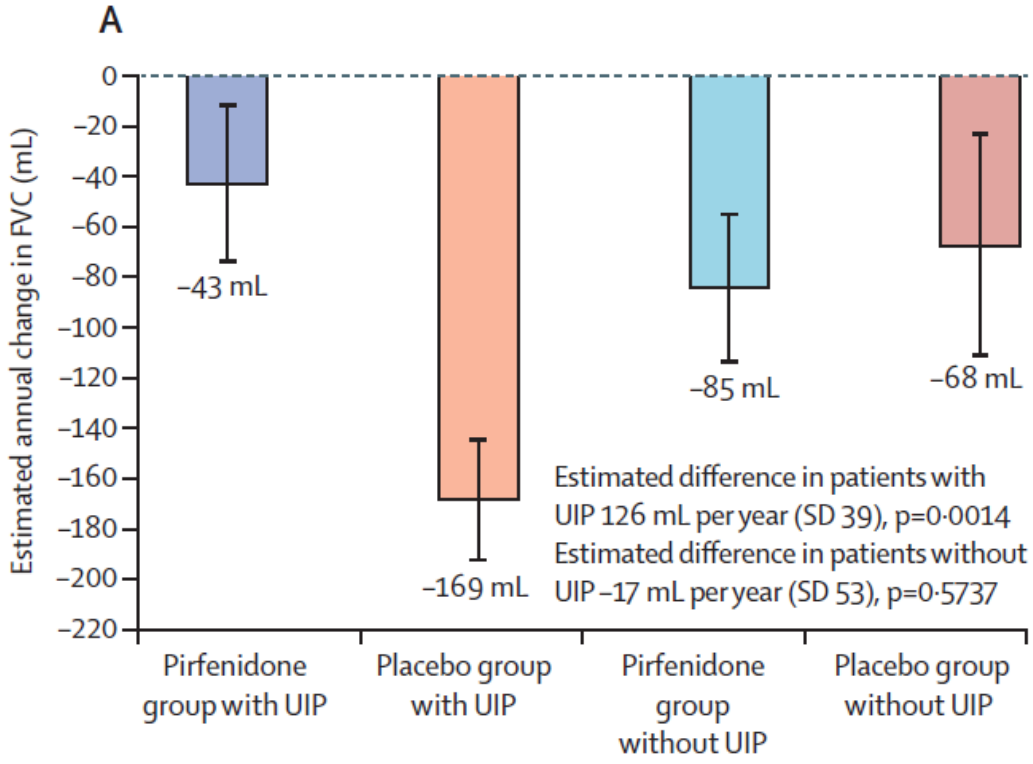


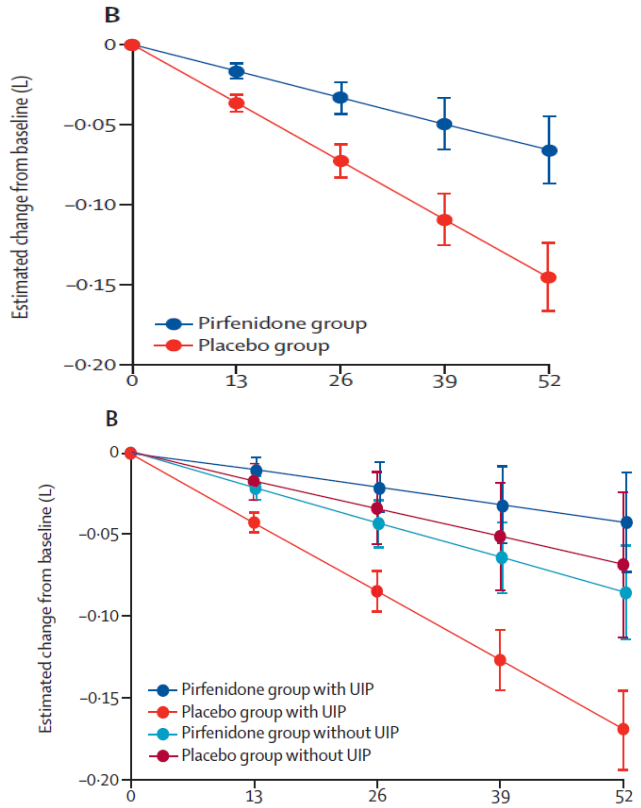
Flaherty KR, et al. N Engl J Med 2019;381:1718-27

Safety and Efficacy of Pirfenidone in RA-ILD

Phase 2, TRAIL1 trial







- Primary endpoint: incidence of progression (FVC decline from baseline ≥10%) or death during 52 weeks → not significant
- Pirfenidone was found to have no new safety signals and slowed decline of FVC over time in subjects with RA-ILD.
- This effect was more pronounced in those with a UIP pattern on baseline HRCT.
- No significant difference in the rate of treatment-emergent serious adverse events between the two groups

JJ Solomon et al, Lancet Respir Med. 2022 :S2213-2600.

FDA Approved Drugs for CTD-ILD

- **Nintedanib for CTD-ILD as a PF-ILD: MAR 2020**

FDA NEWS RELEASE

FDA Approves First Treatment for Group of Progressive Interstitial Lung Diseases

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For Immediate Release: March 09, 2020

The U.S. Food and Drug Administration today approved Ofev (nintedanib) oral capsules to treat patients with chronic fibrosing (scarring) interstitial lung diseases (ILD) with a progressive phenotype (trait). It is the first FDA-approved treatment for this group of fibrosing lung diseases that worsen over time.

"The FDA continues to encourage the development of therapies for patients with limited or no treatment options," said Banu Karimi-Shah, M.D., acting deputy director of the Division of Pulmonary, Allergy, and Rheumatology Products in the FDA's Center for Drug Evaluation and Research. "Today's approval helps to fulfill an unmet treatment need, as patients with these life-threatening lung diseases have not had an approved medication until now."

- **Tocilizumab for SSc-ILD : MAR 2021**

11-03-2021 | Systemic sclerosis | News

approvalsWatch

FDA approves tocilizumab for SSc-ILD

Author: Claire Barnard

medwireNews: Tocilizumab has been approved by the US FDA for slowing the rate of decline in respiratory function in patients with systemic sclerosis (SSc)-associated interstitial lung disease (ILD).

Previously approved for a number of indications including rheumatoid arthritis, giant cell arteritis, and juvenile idiopathic arthritis, the interleukin-6 receptor inhibitor may now be given to adult patients with SSc-ILD at a dose of 162 mg once weekly by subcutaneous injection.

This expanded indication is based on findings from the phase 3 focuSSced trial, in which tocilizumab did not significantly improve skin fibrosis in patients with diffuse cutaneous SSc, but those treated with the agent had a significantly smaller decline in lung function than those given placebo.

The prescribing information for tocilizumab notes that the intravenous formulation has not been approved for SSc-ILD, and that dose interruption may be required for the management of laboratory abnormalities such as neutropenia, thrombocytopenia, and elevated liver enzymes.

When to Start Treatment for ILD

Extensive disease

- ≥20% on HRCT or
- Clinical disease progression evidenced by either or both of the following:
  - 10% FVC decline
  - 5%–9% FVC decline with a 15% DLCO decline

Less extensive disease

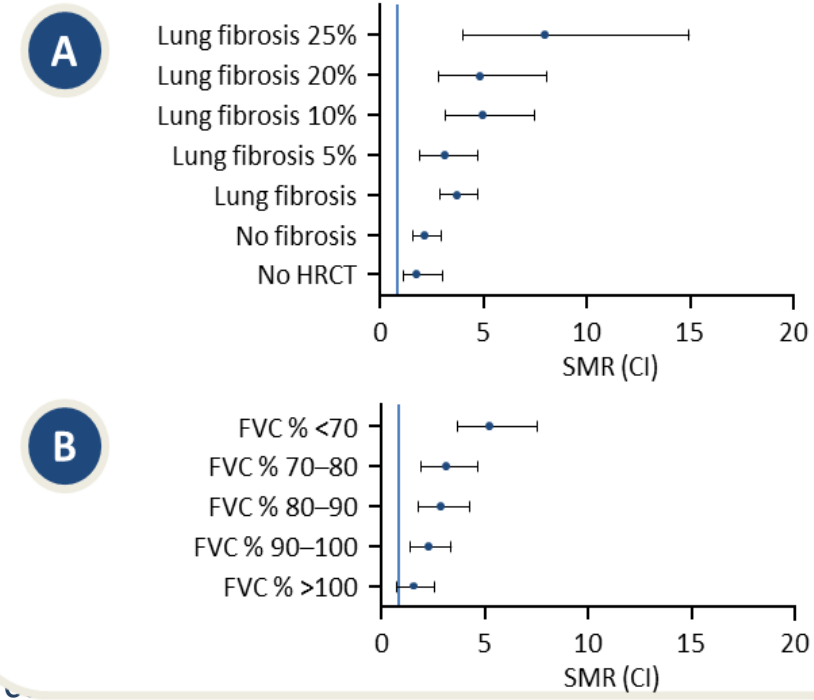
- Risk factors for progression

Perelas A et al. Lancet Respir Med. 2020;8:304–20.

Data Supporting Early Tx of CTD-ILD

- **Norwegian SSc cohort (N=106)**

Standard mortality rate (SMR) by baseline
A) extent of lung fibrosis and **B**) FVC % predicted



SMR ranged from 2.2 in patients with no fibrosis to 8.0 in patients with >25% lung fibrosis

Increased mortality evident in patients with FVC 90–100% at baseline

- Observational study of patients **with early RA** (<2 years since diagnosis)

72% of patients had **abnormal findings** on the HRCT at baseline; median time since RA diagnosis was 3 months

	Abnormalities on HRCT (n=60)*	No abnormalities on HRCT (n=19)*	*P*
FVC % predicted, mean (SD)	95.6 (1.69)	103.6 (2.91)	**0.022**
Abnormal physical examination, n (%)†	13 (21.6)	0 (0)	**0.026**

Paulin F et al. Adv Rheumatol 2021;61:52

Considerations in Management of CTD-ILDs

- Diagnosis
- Severity of ILD
- Evidence of progression
- Risk factors for progression
- Other disease manifestations and comorbidities
- Patient's preferences

Wijsenbeek M, Cottin V. N Engl J Med 2020;383:958-68; Hoffmann-Vold AM et al. Lancet Rheumatol 2020;2:E71–83;
George PM et al. Lancet Respir Med 2020;8:925-934; Ryerson CJ et al. Eur Respir J 2021: 2100276. .

Multidisciplinary Care Team of Kyung Hee ILD Cohort

- 2018년부터 환자 등록을 시작, 1년마다 & 악화시 데이터 수집
- 현황: CTD-ILD 117명 (RA-ILD 50명), 특발성 ILD 119명

KH-ILD Cohort

Rheumatology

- CTD-ILD
  - SSc, PSS, RA, SLE, MCTD, overlap syndromes
  - IIM(DM,PM), AAV(GPA, MPA, EGPA)

Pulmonology

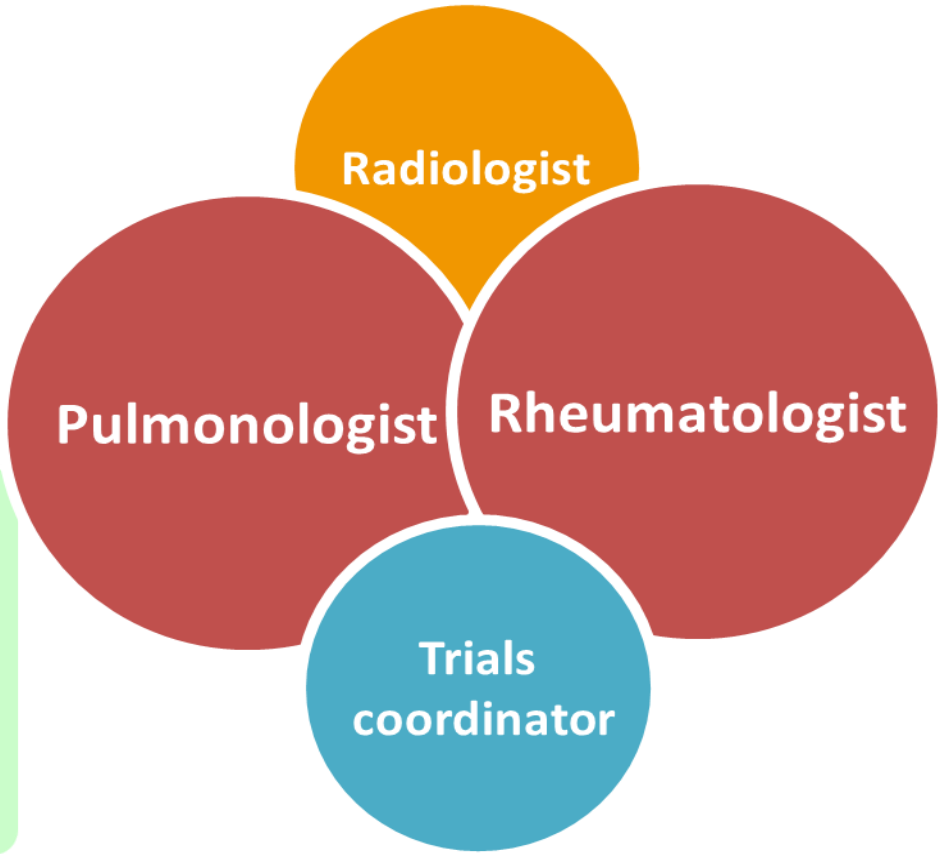
- Idiopathic ILD
  : NSIP, OP, UIP, LIP, DIP, DPB, DAH

Routine Clinical Measures

- Age, sex, age at the time of Dx of ILD
- Hx: smoking, Tb
- Medication list
- Lab: ESR, CRP, LDH
- PFT including DLco, 6 min walking test
- HRCT pattern
  : NSIP, OP, UIP, LIP, DIP, DPB
- Histopathology(optional)

연구를 위한 수집

- 관련증상 탐색
  : 레이노, 구강건조증 역증성 관절염
- AutoAb Screening
- 관련 유전자 및 biomarker 탐색을 위한 혈액채취
  : Whole blood 3CC (EDTA), Serum 3cc(SST)
- Nailfold capillaroscopy
- Questionnaire: HAQ, 호흡기능 평가 설문
- Cardiac Echo (optional)



Summary

- ILD는 CTD 환자의 주요 합병증이며, 동반하는 경우 morbidity, mortality 증가
- HRCT, Serologic test 등을 통한 CTD-ILD 의 조기 진단 및 적극적 치료→ 예후개선
- ILD 환자에서 자가면역질환 동반을 의심해야 하는 단서

  : 레이노현상, 수지궤양, 피부병변, 관절염, 근육관련 증상 및 근효소 상승, Sicca symptoms
- Better Prognosis: CTD-ILD > IPF, NSIP/OP > UIP, Lesser extent > Extensive disease
- Paradigm shift in treatment strategies.
  - Anti-IL-6, Abatacept, Rituximab 등 Non-TNF biologics 가 favorable result 를 보여주고 있음
  - CTD-ILD 치료로 antifibrotic agent 역할 대두: Optimal initiation timing, Immune suppressant + Antifibrotic agent combination strategy 에 대한 연구 필요