

ILD 환자에서 자가면역질환의 진단적 접근

Eun Young Lee

Division of Rheumatology, Department of Internal Medicine
Seoul National University College of Medicine



SNU MEDICINE

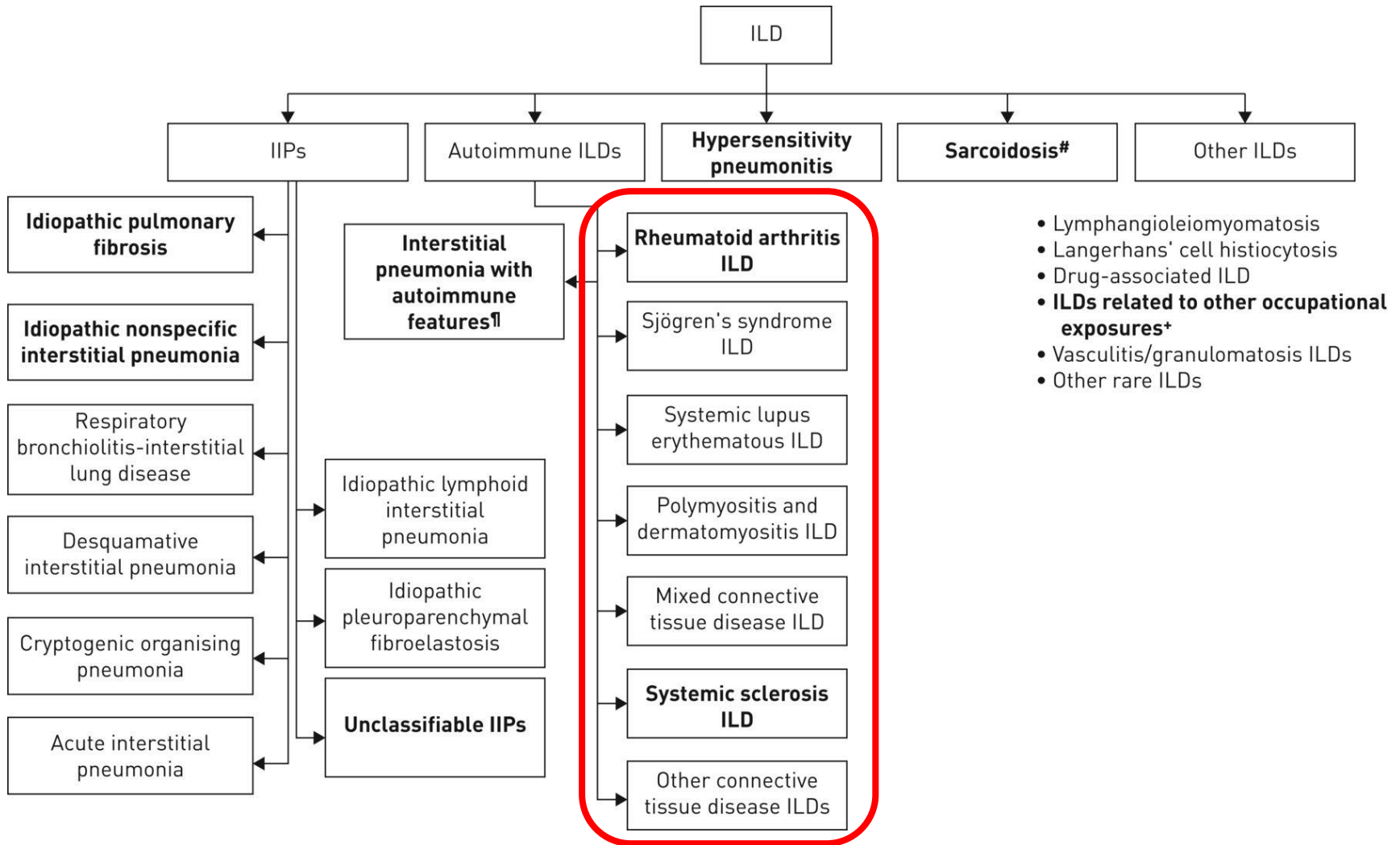
Seoul National University College of Medicine

Contents

- Autoimmune diseases associated with ILD
 - Approach
 - Diagnosis
- Rheumatoid arthritis with ILD
 - Clinical course of disease
 - Medical treatment of RA
 - Prognosis of RA/ILD
 - Introduction of KORAIL cohort



Autoimmune ILDs



Approach to the management of CTD-ILD

- Most connective tissue diseases
 - Chronic course of the disease and have various comorbidities
 - Each disease show variable, wax and wane course
 - High risk of infection
 - Multiple medication including systemic glucocorticoids or immunosuppressive agents
- Understanding about the exact **diagnosis** and expected **disease course** of the underlying connective tissue disease
- Clinical suspicion is important!



CTD-ILD association:

Rheumatic diseases and Interstitial lung disease, unwelcome friends?

- major CTDs: systemic sclerosis (SSc), rheumatoid arthritis (RA), polymyositis–dermatomyositis (PM/DM), systemic lupus erythematosus (SLE), primary Sjögren syndrome (pSS), mixed connective tissue disease (MCTD)
- Prevalence rates ?
 - SSc 25-90%
 - RA 2-63%
 - PM/DM 5-70%
 - SLE 3-38%



Pulmonary manifestations of autoimmune diseases

Table 2.1 Most common CTD-associated pulmonary manifestations

	SSc	RA	Primary Sjögren's	MCTD	PM/DM	SLE
Airways	-	++	++	+	-	+
ILD	+++	++	++	++	+++	+
Pleural	-	++	+	+	-	+++
Vascular	+++	-	+	++	+	+
DAH	-	-	-	-	-	++

The number of + signs indicates relative prevalence of each manifestation

SSc systemic sclerosis, *RA* rheumatoid arthritis, *CTD* connective tissue disease, *MCTD* mixed connective tissue disease, *PM/DM* polymyositis/dermatomyositis, *SLE* systemic lupus erythematosus, *ILD* interstitial lung disease, *DAH* diffuse alveolar hemorrhage

Used with permission from Fischer A, du Bois RM. A Practical Approach to Connective Tissue Disease-Associated Lung Disease. In Baughman RP, duBois RM (eds): Diffuse Lung Disease: A Practical Approach. 2nd ed. New York: Springer; 2012



Histological patterns of CTD-ILDs

Table 1 | The relative prevalence of histological patterns in IIP in CTDs

Lung pattern	IIP	Rheumatoid arthritis	Systemic sclerosis	SLE	Polymyositis-dermatomyositis	Sjögren syndrome
Usual interstitial pneumonia	+++	++	+	+	+	±
Nonspecific interstitial pneumonia	++	++	+++	++	++	++
Desquamative interstitial pneumonia and/or RB-ILD	+	±	±	±	±	±
Organizing pneumonia	++	+	±	±	++	±
Lymphocytic interstitial pneumonia	±	±	±	±	±	++
Pleuroparenchymal fibroelastosis	±	?	?	?	?	?
Diffuse alveolar damage	+	+	±	+	+	±

Abbreviations: ?, prevalence unknown; ±, rare; +, infrequent; ++, frequent, but not clearly in the majority of cases; +++, common, clearly in the majority of cases; CTD, connective tissue disease; IIP, idiopathic interstitial pneumonia; RB-ILD, respiratory bronchiolitis-associated interstitial lung disease; SLE, systemic lupus erythematosus.



TABLE 1 | Rheumatic Diseases and Their Associated Historical and Physical Findings, Imaging Features, and Serologic Characteristics

Rheumatic Disease	Historical and Physical Findings	Common Imaging Features	Typical Serologic Characteristics	
			Autoantibody	Special Consideration
SSc/ scleroderma	Raynaud syndrome, gastroesophageal reflux disease, calcinosis cutis, skin thickening, ulcers on the fingertips, limited oral aperture, nail fold capillary microscopic abnormalities, pericarditis	NSIP UIP OP AIP/DAD DAH	ANA	Nucleolar pattern, anticentromere pattern
			SCL-70, TH/TO, RNA polymerase III, U3 RNP	...
AIM	Dysphagia, proximal muscle weakness, photosensitive rash on hands/chest/face/back, mechanic hands, antisynthetase syndrome (Raynaud syndrome, mechanic hands, fever, arthritis, ILD)	NSIP OP UIP AIP/DAD Pneumomediastinum	Creatinine kinase, aldolase	...
			MDA5	Skin nodules, dermatomyositis, and ILD
			Jo-1, PL-12, PL-7 OJ, EJ, ZO, KS	Antisynthetase syndrome
			Anti-PM/SCL, Ku	Seen with overlap of myositis and SSc
Rheumatoid arthritis	Swollen joints in the hands (especially wrists, MCP joints), knees, and feet (including the MTP joints); rheumatoid nodules; inflammatory eye disease	UIP NSIP OP Bronchiolitis Lung nodules	Anti-Ro/SSA	Ro 52-kD associated with AIM and SSc and ILD
			RF	Higher rate of false positive results with RF alone
			Anticyclic citrullinated peptides	...
SLE	Joint pain, alopecia, oral ulcers, pleurisy, rash, photosensitivity, pericarditis	Acute pneumonitis NSIP/UIP DAH OP	Anti-Smith	...
			Anti-Ro/SSA Anti-La/SSB	Ro 52-kD associated with SSc and AIM and ILD
Sjögren syndrome	Dry eye and mouth, parotid swelling (Fig 4 C), neuropathy	LIP Follicular bronchiolitis Cystic lung disease NSIP UIP OP	Anti-Ro/SSA Anti-La/SSB	...

Rheumatic Disease	Historical and Physical Findings	Common Imaging Features	Typical Serologic Characteristics	
			Autoantibody	Special Consideration
			RF	...
Mixed connective tissue disease	Variable signs and symptoms primarily associated with SLE, SSc, and AIM	NSIP LIP	ANA	Nuclear speckled pattern
			Anti-RNP Ribonucleoprotein	Features of different rheumatic diseases/ mixed connective tissue disease including SSc, AIM, SLE, with higher risk of ILD and PAH
Vasculitis	Palpable purpura, necrotic skin lesions, otitis media, epistaxis, nasal septal perforation, mononeuritis multiplex, hemoptysis, oral ulcers	DAH UIP	ANCA	GPA, MPA, and EGPA
			Antiglomerular basement membrane	
			RF	GPA, cryoglobulinemia



Screening of ILD for specific rheumatic diseases

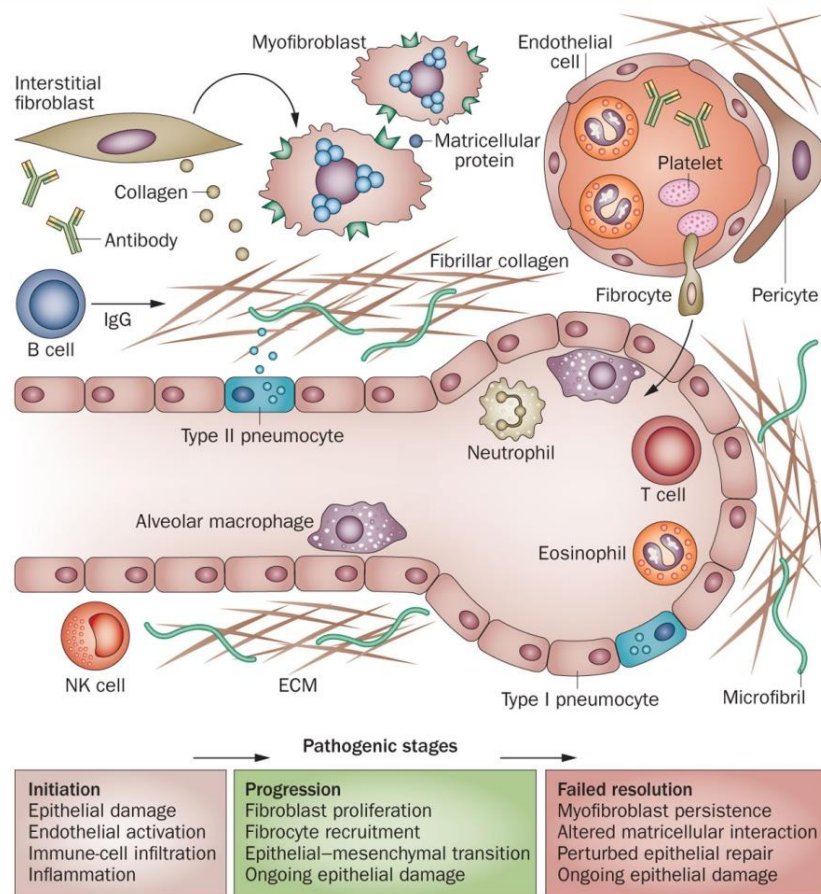
TABLE 3] Options for Screening and Treatment of ILD for Specific Rheumatic Diseases

Rheumatic Disease	Screening	Treatment
SSc	Baseline PFTs, HRCT, and echocardiography for all patients; if normal, yearly PFTs. If there is a decline in FVC > 10% or D _{lco} > 15% consider repeated CT imaging and echocardiography. Consider treatment in any patient with fibrotic lung disease > 20% on HRCT (extensive); if < 20%, PFTs every 3-6 mo.	MMF: Use up to 3 g/d CyC: An option for 6-9 mo with conversion to MMF or AZA In early rapidly progressive disease, consider suitability for stem cell transplantation at selected centers
AIM	Baseline PFTs and HRCT in all patients. If CT results are abnormal and patient is symptomatic with FVC < 70%, consider treatment. If patient is not symptomatic with FVC > 70%, PFTs every 3-6 mo.	For moderate disease: MMF, AZA, or tacrolimus with steroids Rituximab should be considered in antisynthetase syndrome In MDA5-ILD, aggressive therapy including high-dose glucocorticoids and at least 1 other steroid-sparing agents such as CyC, Rituxan or MMF should be used
Rheumatoid arthritis	Baseline PFTs in high-risk individuals (smokers, male sex, older age). If abnormal results, consider HRCT	If predominantly inflammatory disease, MMF or rituximab If predominantly fibrotic disease, consider antifibrotic agents pending results from ongoing trials

AZA = azathioprine; CyC = cyclophosphamide; D_{lco} = diffusion capacity for carbon monoxide; HRCT = high-resolution CT; MDA5 = melanoma differentiation-associated gene 5; MMF = mycophenolate mofetil; PFTs = pulmonary function tests. See Table 1 legend for expansion of other abbreviations.



Figure 1 Cellular pathogenesis of fibrotic lung injury



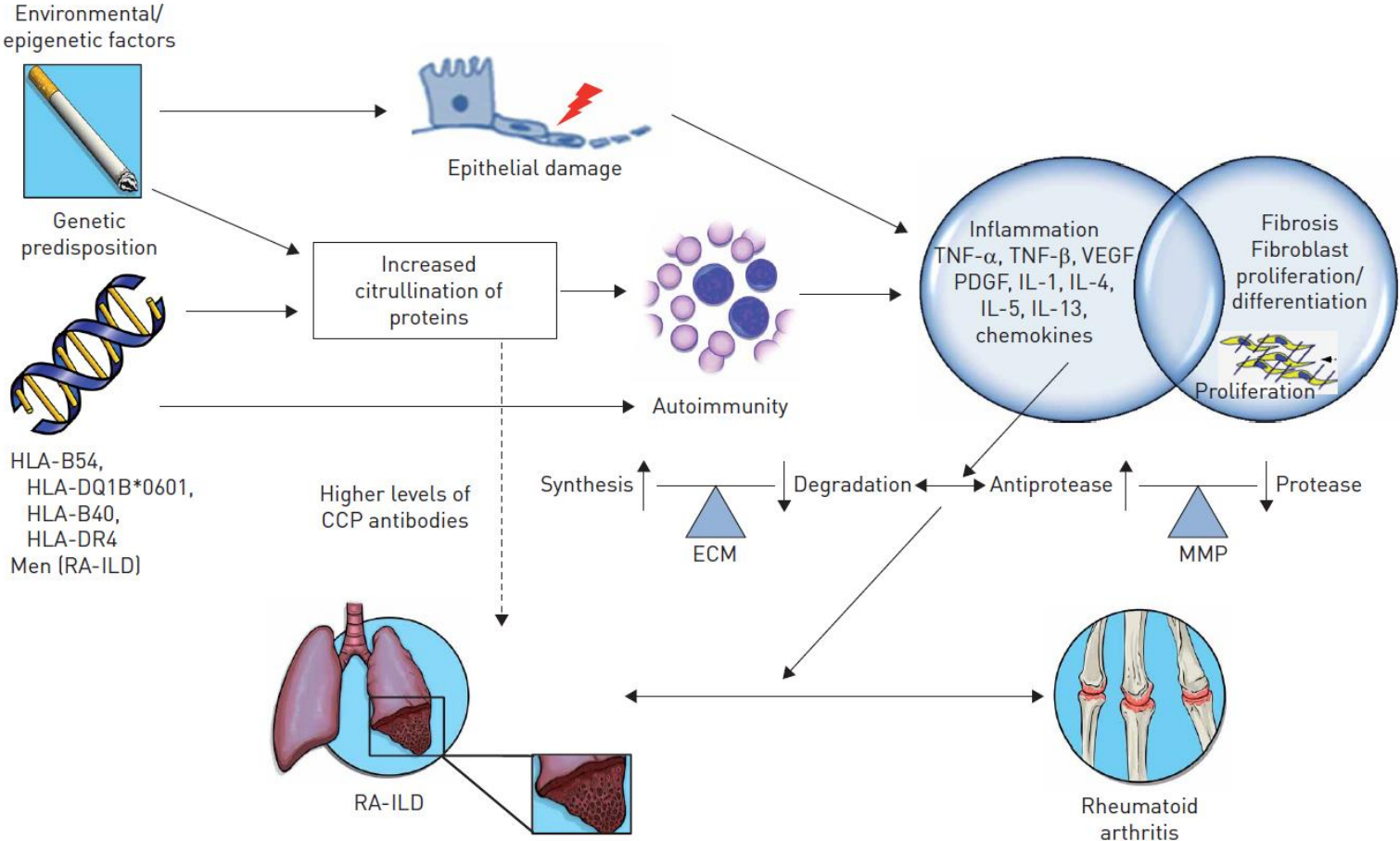
Wells, A. U. & Denton, C. P. (2014) Interstitial lung disease in connective tissue disease—mechanisms and management
Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2014.149

Pathogenesis, esp. SSc-ILD

- **Inflammation, epithelial damage** -> TGF- β
- **Effector cells:** activated fibroblasts and myofibroblasts
 - > produce ECM proteins, fibrogenic scarring
- **Epithelial damage:** fast diethylenetriamine penta-acetate (DTPA) clearance and high KL-6 serum levels
- **Autoantibodies:**
 - anti-topoisomerase antibodies (high risk of lung disease)
 - anti-RNA polymerase III antibodies (less lung disease)
 - anti-U11/U12 ribonucleoprotein (RNP) antibodies or anti-Th/To RNP antibodies (high risk)
- **Genetics:** *CTGF* polymorphism, CD247 and IRF5 from GWAS study, IL-6 associated gene



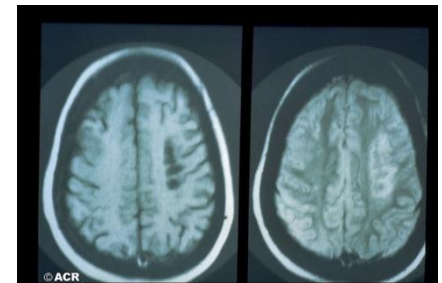
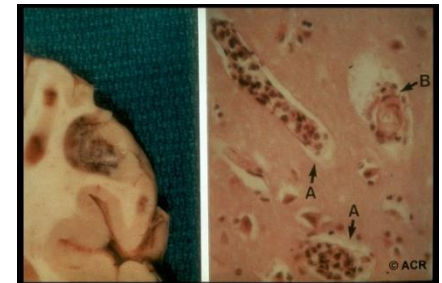
RA and ILD, shared genetic and immunologic component



SLE

1. Malar rash	Fixed erythema, flat or raised, over the malar eminences
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur
3. Photosensitivity	Exposure to <u>UV</u> light causes rash
4. Oral ulcers	Includes oral and nasopharyngeal, observed by physician
5. Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	Pleuritis or pericarditis documented by ECG or rub or evidence of pericardial effusion
7. Renal disorder	Proteinuria > 0.5 g/d or > 3+, or cellular casts
8. Neurologic disorder	Seizures without other cause or psychosis without other cause
9. Hematologic disorder	Hemolytic anemia or leukopenia (< 4000/ ^μ L) or lymphopenia (< 1500/ ^μ L) or thrombocytopenia (< 100,000/ ^μ L) in the absence of offending drugs
10. Immunologic disorder	Anti-dsDNA, anti-Sm, and/or anti-phospholipid
11. Antinuclear antibodies	An abnormal titer of <u>ANAs</u> by immunofluorescence or an equivalent assay at any point in time in the absence of drugs known to induce ANAs

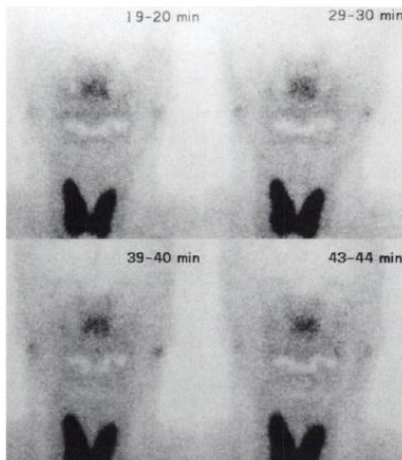
If four of these criteria are present at any time during the course of disease, a diagnosis of systemic lupus can be made with 98% specificity and 97% sensitivity.



Primary SjS

- 2012 ACR criteria for SjS-

- At least 2 of the 3 objective features
 - Anti-SSA/Ro and/or anti-SSB/La or (positive RF & ANA \geq 1:320)
 - Labial salivary gland biopsy: focal score \geq 1 /4 mm²
 - Keratoconjunctivitis sicca with ocular staining score \geq 3
- Exclusion of the following conditions
 - Head & neck radiation, HCV infection, HIV infection, sarcoidosis, amyloidosis, Graft versus host disease, IgG4-related disease
- Abandon the concept of primary versus secondary SjS.



SNU MEDICINE

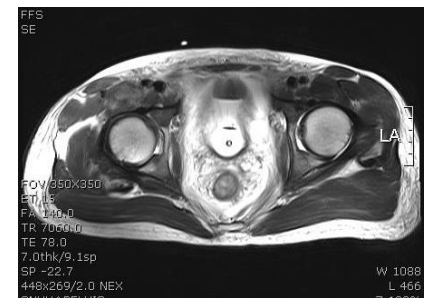
Seoul National University College of Medicine

Idiopathic inflammatory myopathy

- Bohan & Peter Criteria (1975)
 - Symmetric proximal muscle weakness
 - Muscle biopsy evidence of myositis
 - Elevated muscle enzymes
 - Characteristic electromyographic (EMG) pattern
 - Typical rash of DM

definite PM : all of the above 1-4 criteria

definite DM : any 3 of 1-4 criteria plus skin rash



2010 RA Classification Criteria

Table 3. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis

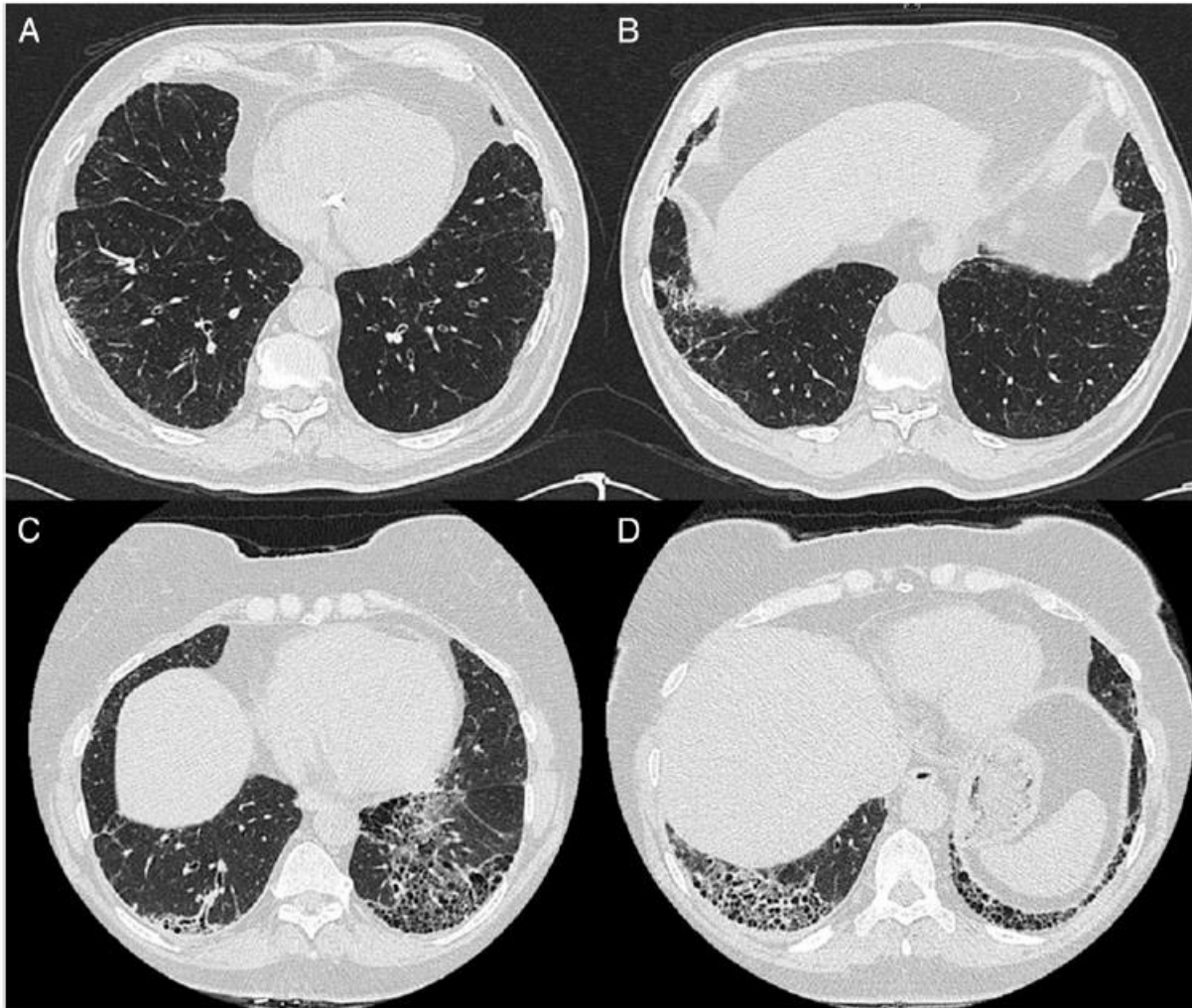
	Score
Target population (Who should be tested?): Patients who	
1) have at least 1 joint with definite clinical synovitis (swelling)*	
2) with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of $\geq 6/10$ is needed for classification of a patient as having definite RA)‡	
A. Joint involvement§	
1 large joint¶	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)#	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)**	5
B. Serology (at least 1 test result is needed for classification)††	
Negative RF <i>and</i> negative ACPA	0
Low-positive RF <i>or</i> low-positive ACPA	2
High-positive RF <i>or</i> high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)‡‡	
Normal CRP <i>and</i> normal ESR	0
Abnormal CRP <i>or</i> normal ESR	1
D. Duration of symptoms§§	
<6 weeks	0
≥ 6 weeks	1



ILD in RA

- most common pulmonary manifestation of RA lung disease
- Prevalence
 - variable (population and diagnostic modality, 2~63%)
 - ~ 30% of patients with RA have subclinical ILD on HRCT
 - Stable prevalence even after development of RA Tx modality

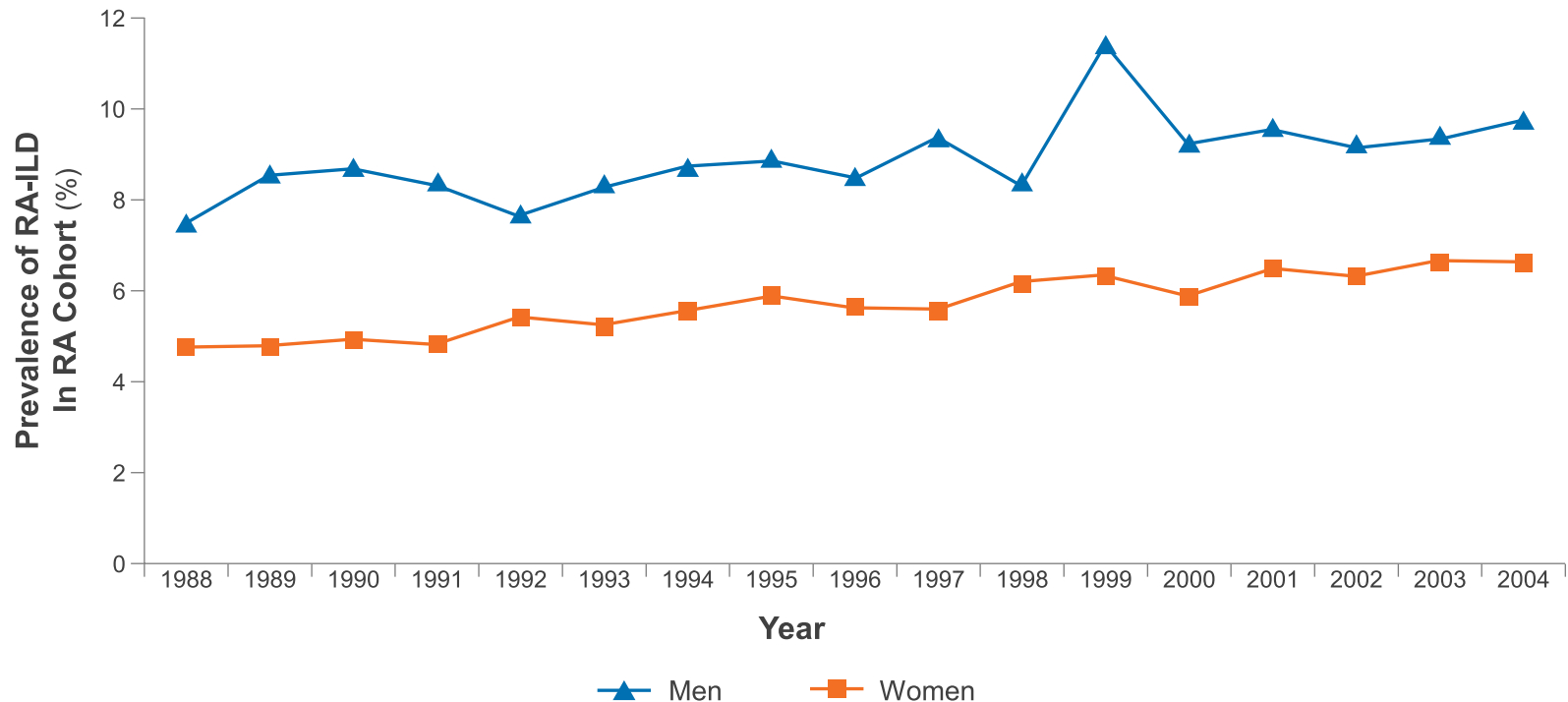




- A, B subclinical ILD in RA
- C, D clinical ILD in RA

Increasing Burden of RA-ILD

- ILD occurs in 10% of the RA population.
- Burden of RA-ILD is increasing and is associated with shortened survival



Epidemiology/Risk factors

- more frequently in males
- male to female ratio as high as 2:1
- Onset: fifth to sixth decade of life

- Old age
- history of smoking (odds ratio of 3.8 for those who smoked >25 pack-years)
- High levels of rheumatoid factor



British rheumatoid interstitial lung (BRILL) network

TABLE 1 Factors associated with ILD in patients with RA

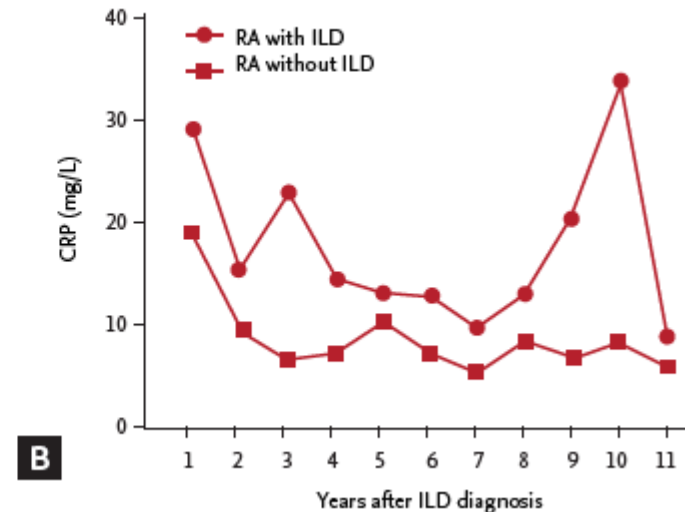
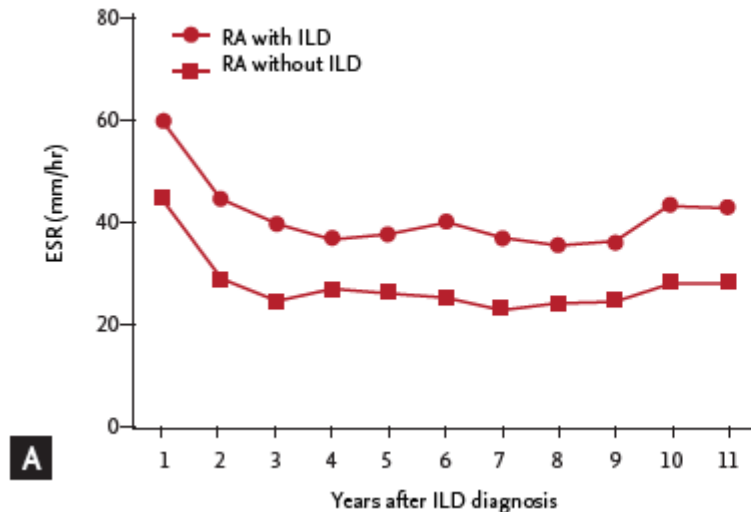
Factor	RA-ILD patients	Control RA patients	P-value
Patients, <i>n</i>	230	230	
Smoking, %			
Males ever	75	60	0.02
Females ever	60	59	0.92
Total male pack-years, median (range)	35 (15-120)	21 (5-60)	0.01
Total female pack-years, median (range)	20 (10-80)	20 (5-75)	0.96
Serology			
RF, %	89	58	0.01
CCP antibody, %	94	55	0.006
CCP antibody titres, median (range)	180 (8-340)	78 (8-340)	0.02

- Anti-CCP antibodies were strongly associated with RA-ILD
- Smoking was strongly associated with ILD in males
-> higher frequency of RA-ILD in men
- predominant HRCT pattern was UIP



RA-ILD in SNUH

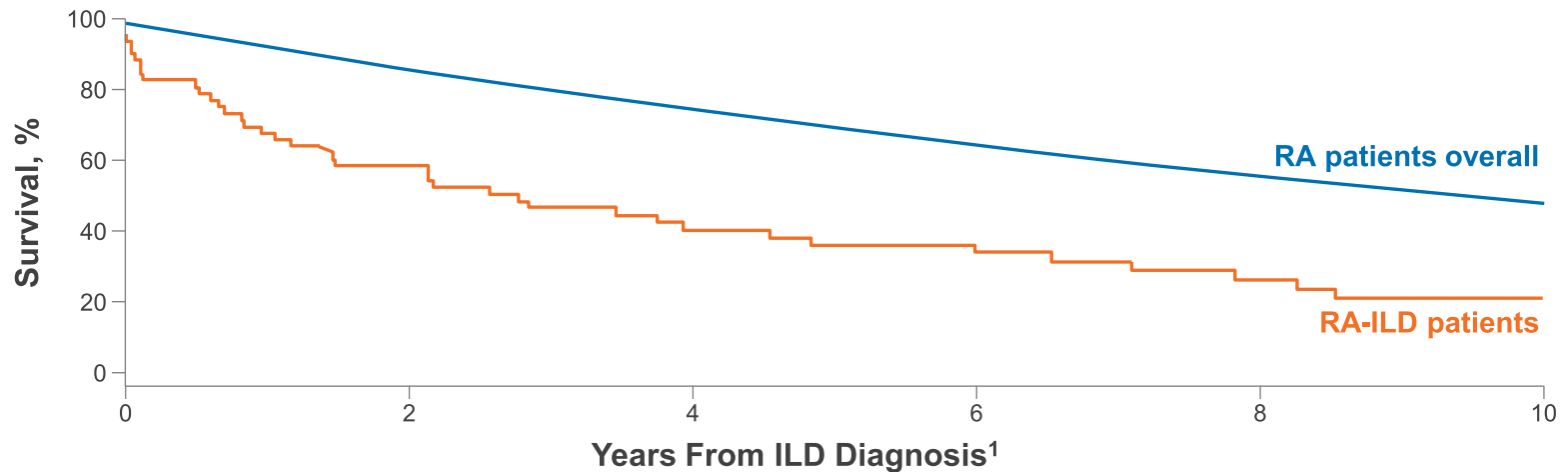
- Retrospective review of medical records, single center
- 77 rheumatoid arthritis (RA) patients with interstitial lung disease (ILD), 10 year follow-up



Higher inflammatory burden at any time of disease -> may require more steroid therapy

ILD Confers a High Mortality Burden on RA Patients

- The median survival for patients with clinical RA-ILD is **2.6 years**
 - Reduced by 7.3 years vs RA non-ILD¹
- The adjusted HR of death for RA-ILD is **1.9 to 10.4 times greater** vs RA-non-ILD²
- Age, RA disease duration at ILD diagnosis, and DL_{CO} values were strongly associated with ILD mortality³

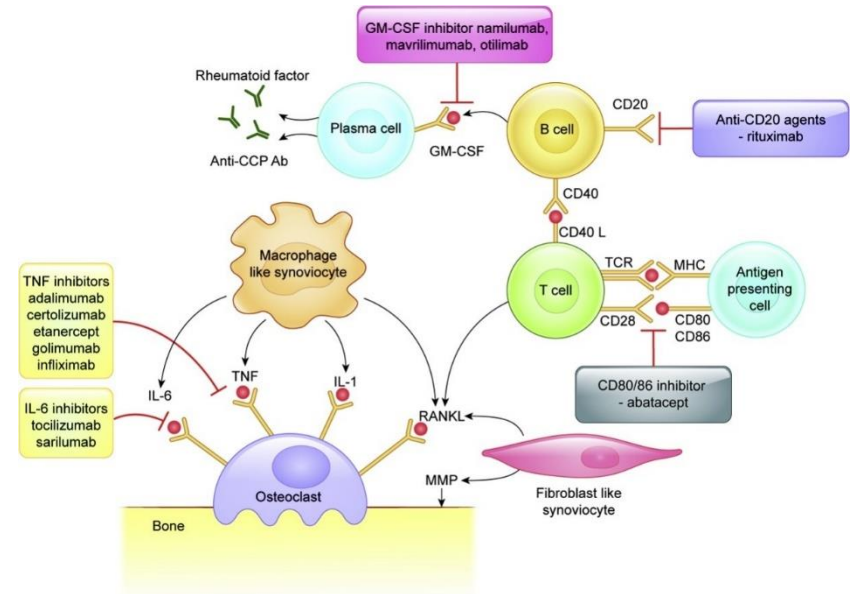
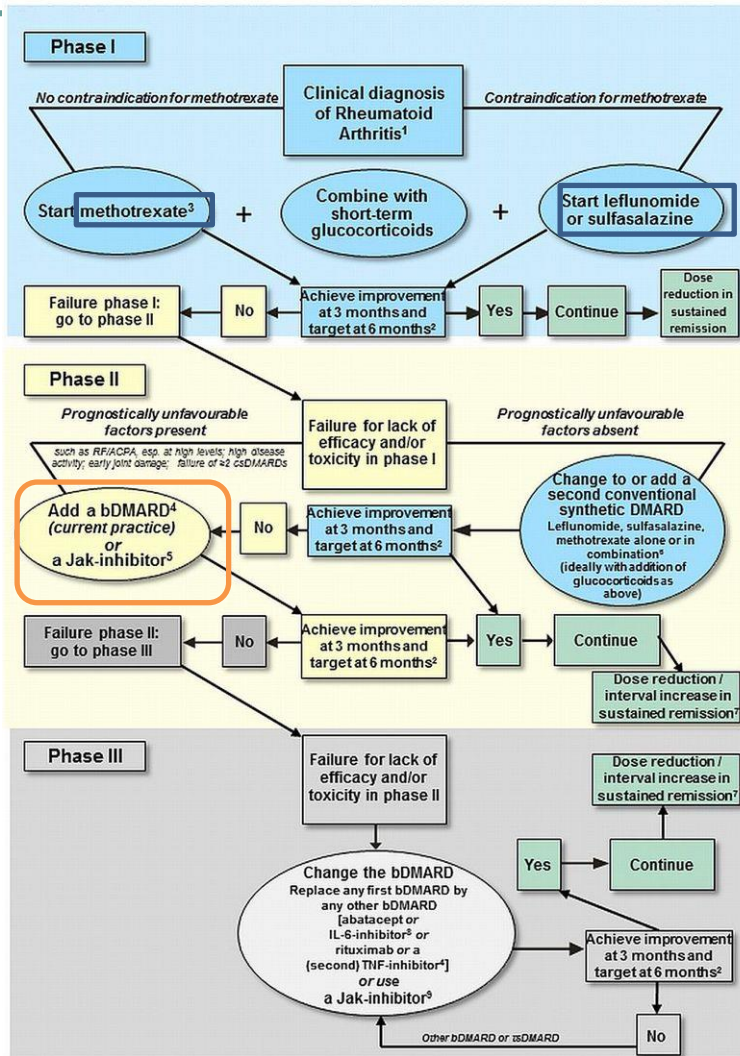


Management

- Treatment is **focused on RA** with anti-inflammatory and/or immunosuppressive agents -> **DMARDs** (disease modifying antirheumatic drugs)
- no randomized controlled trials comparing medications for the treatment of RA lung disease.
- **Glucocorticoids**
 - mainstay of therapy, esp NSIP or BOOP
 - May induce regression of consolidation
- **DMARDs**
 - Methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, ..
 - Combination or monotherapy
- Cyclophosphamide, azathioprine, cyclosporine, mycophenolate mofetil for CTD-ILD



Treatment guidelines RA – pharmacologic Tx



¹2010 ACR-EULAR classification criteria can support early diagnosis. ²The treatment target is clinical remission according to ACR-EULAR definition or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if no sufficient improvement is seen after 3 months. ³Methotrexate should be part of the first treatment strategy², while combination therapy of csDMARDs is not preferred by the Task Force, starting with methotrexate does not exclude its use in combination with other csDMARDs. ⁴TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved tsDMARDs), abatacept, IL-6-inhibitors, or rituximab; in patients who cannot use csDMARDs as comedication, IL-6-inhibitors and tsDMARDs have some advantages. ⁵Current practice would be to start with a bDMARD (in combination with MTX or another csDMARD) because of the long-term experience compared with tsDMARDs (Jak-inhibitors). ⁶The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychloroquine. ⁷Dose reduction or interval increase can be safely done with all bDMARDs with little risk of flares; stopping is associated with high flare rates; most but not all patients can recapture their good state upon re-institution of the same bDMARD. ⁸Efficacy and safety of bDMARDs after Jak-inhibitor failure is unknown; also, efficacy and safety of an IL-6 pathway inhibitor after another one has failed is currently unknown. ⁹Efficacy and safety of a Jak-inhibitor after insufficient response to a previous Jak-inhibitor is unknown.



Methotrexate induced lung toxicity

Bone marrow toxicity

Neutropenia (most common, usually reversible)

Thrombocytopenia (dose related, usually reversible)

Anemia (rare)

Hepatic toxicity

Cirrhosis & fibrosis

Pulmonary toxicity

Opportunistic infections

PCP, CMV, Herpes zoster, fungal, mycobacterial, etc

Noninfectious conditions

Hypersensitivity pneumonitis

Organizing pneumonia (previously called bronchiolitis obliterans with organizing pneumonia or BOOP)

Acute lung injury (noncardiogenic pulmonary edema)

Pulmonary fibrosis

Asthma/hyperreactive airways disease

Pleuritis and/or pleural effusion

Miscellaneous

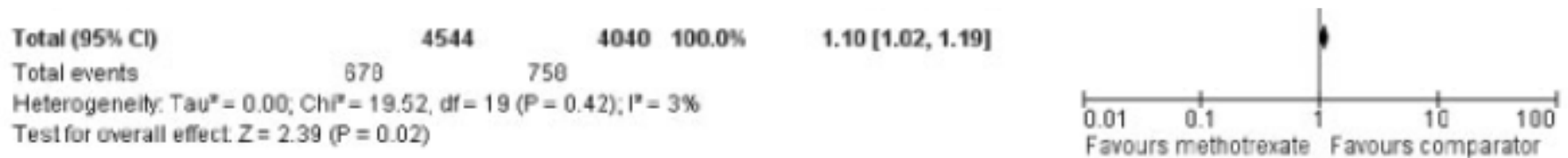
Oligospermia

Teratogenicity

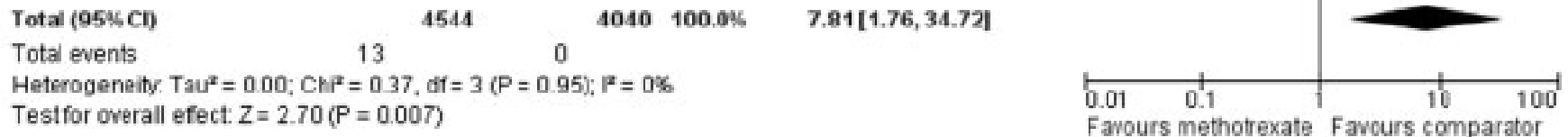
Malignancy

MTX-induced lung disease

- Incidence: 3.5-7.6%, Prevalence: 5%
- Relative risk of total respiratory adverse events between MTX with comparator



- Relative risk of pneumonitis between MTX with comparator



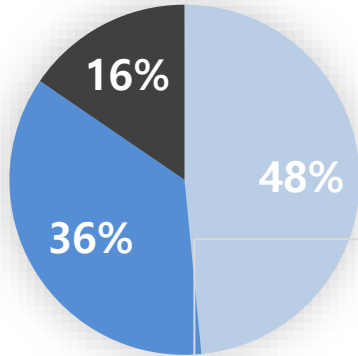
Do DMARDs cause lung toxicity?

- no definite evidence that MTX leads to progression of ILD, but MTX has potential lung toxicity
- (Sulfasalazine), **leflunomide**, etanercept, infliximab, adalimumab, and (rituximab, tocilizumab) all have been “ associated” with **lung toxicity**
- Occur far less commonly or convincingly than with MTX
- Far fewer data to confirm a direct causal effect
 - scattered case reports suggest a possible association



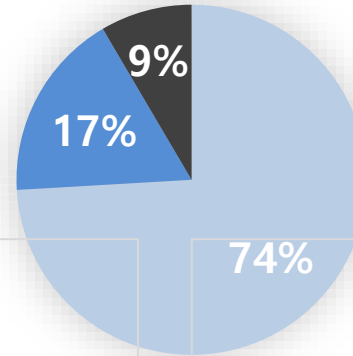
How about bDMARDs?

Anti-TNF α blockers



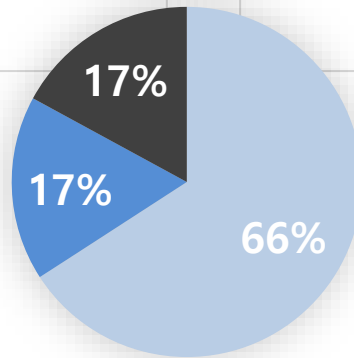
■ 호전 ■ 유지 ■ 악화

Abatacept

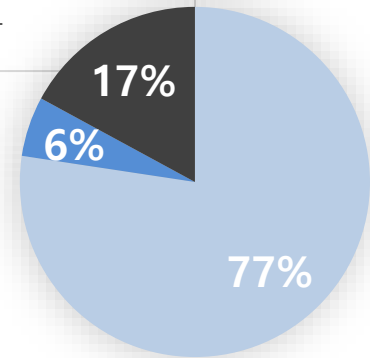


■ 호전 ■ 유지 ■ 악화

Tocilizumab



Rituximab



연구에 따라 결과가 상이함. 증례보고, 후향적연구, 시판 후 조사 및 표적치료제 레지스트리를 이용한 연구가 대부분이며 각 연구에서의 증례 수가 300에 이내임.



- The British Society for Rheumatology guideline suggests RTX and ABA as a first-line biologic in RA patients with ILD.



RHEUMATOLOGY

Guidelines

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

Respiratory disease

(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%)



- 류마티스 관절염 연관 간질성 폐질환은 불량한 예후가 예측됨에도 불구하고 아직 정립된 치료 방침이 없음.
- 2018년 호흡기학회 간질성 폐질환 진료지침
- 류마티스 관절염 연관 간질성 폐질환의 치료 권고사항은 아직 근거 및 권고수준이 낮고 전신경화증 연관 간질성 폐질환에서와 같이 구체적인 약제 선택에 대한 가이드는 없음.

권고사항

- 전신경화증 연관 간질성폐질환 환자에서 질환의 진행을 늦추기 위하여 cyclophosphamide 사용을 고려한다 (근거수준: 낮음, 권고수준: 약함)
- 류마티스관절염 연관 간질성폐질환 환자에서 질환의 진행을 막기 위하여 스테로이드 및 면역억제제 사용을 고려한다(근거수준: 전문가 의견, 권고수준: 약함)



Anti-fibrotic agent for CTD/ILD including RA/ILD

- Pirfenidone – fail to show favorable outcome
- Nintedanib
 - Subgroup analyses of INBUILD trial

Nintedanib in patients with progressive fibrosing interstitial lung diseases—subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial

*Athol U Wells, Kevin R Flaherty, Kevin K Brown, Yoshikazu Inoue, Anand Devaraj, Luca Richeldi, Teng Moua, Bruno Crestani, Wim A Wuyts, Susanne Stowasser, Markel Quaresima, Rainer Georg Goeldner, Razsa Schlenker-Herzig, Mart in Kolb on behalf of the INBUILD trial investigators**

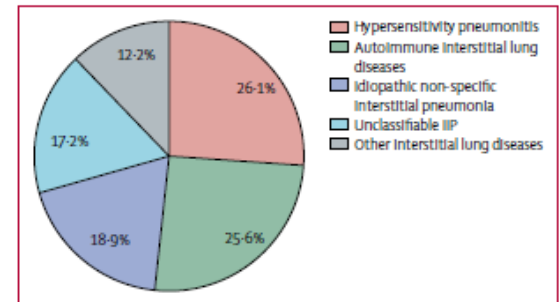


Table S1. Baseline characteristics in 9 subgroups by ILD diagnosis noted in case report form (overall population)

	HP (n=173)	iNSIP (n=125)	Unclassifiable IIP (n=114)	RA-ILD (n=89)	SSc-ILD (n=39)	MCTD-ILD (n=19)	Exposure-related ILDs (n=39)	Sarcoidosis (n=12)	Other fibrosing ILDs* (n=53)
Male, n (%)	89 (51.4)	63 (50.4)	62 (54.4)	54 (60.7)	9 (23.1)	4 (21.1)	36 (92.3)	5 (41.7)	34 (64.2)
Age (years), mean (SD)	65.5 (8.3)	65.4 (9.4)	68.4 (9.4)	66.9 (9.6)	68.4 (10.0)	64.5 (9.5)	69.4 (10.4)	63.1 (14.4)	63.5 (11.0)
Former or current smoker, n (%)	91 (52.6)	43 (34.4)	62 (54.4)	57 (64.0)	8 (20.5)	6 (31.6)	33 (84.6)	4 (33.3)	34 (64.2)
FVC, mL, mean (SD)	2244 (739)	2351 (761)	2286 (730)	2394 (694)	2229 (618)	2082 (407)	2551 (597)	2188 (497)	2588 (931)
FVC, % predicted, mean (SD)	65.2 (14.2)	71.3 (17.3)	69.8 (15.4)	71.5 (16.2)	69.7 (12.7)	71.1 (12.5)	67.9 (14.6)	64.9 (16.8)	70.5 (17.5)
DLco % predicted, mean (SD) [†]	45.3 (14.4)	47.4 (12.5)	45.2 (11.9)	47.7 (15.6)	47.7 (12.9)	51.4 (18.2)	44.9 (14.7)	39.9 (6.0)	44.2 (12.1)

*Comprised “autoimmune ILDs” such as Sjögren’s syndrome and IPAF. †Corrected for haemoglobin.

COP=cryptogenic organising pneumonia. DLco=diffusing capacity of the lung for carbon monoxide. FVC=forced vital capacity. HP=hypersensitivity pneumonitis. IIP=idiopathic interstitial pneumonia. ILD=interstitial lung disease. iNSIP=idiopathic non-specific interstitial pneumonia. IPAF=interstitial pneumonia with autoimmune features. MCTD=mixed connective tissue disease. PPFE=pleuroparenchymal fibroelastosis. RA=rheumatoid arthritis. SSc=systemic sclerosis.



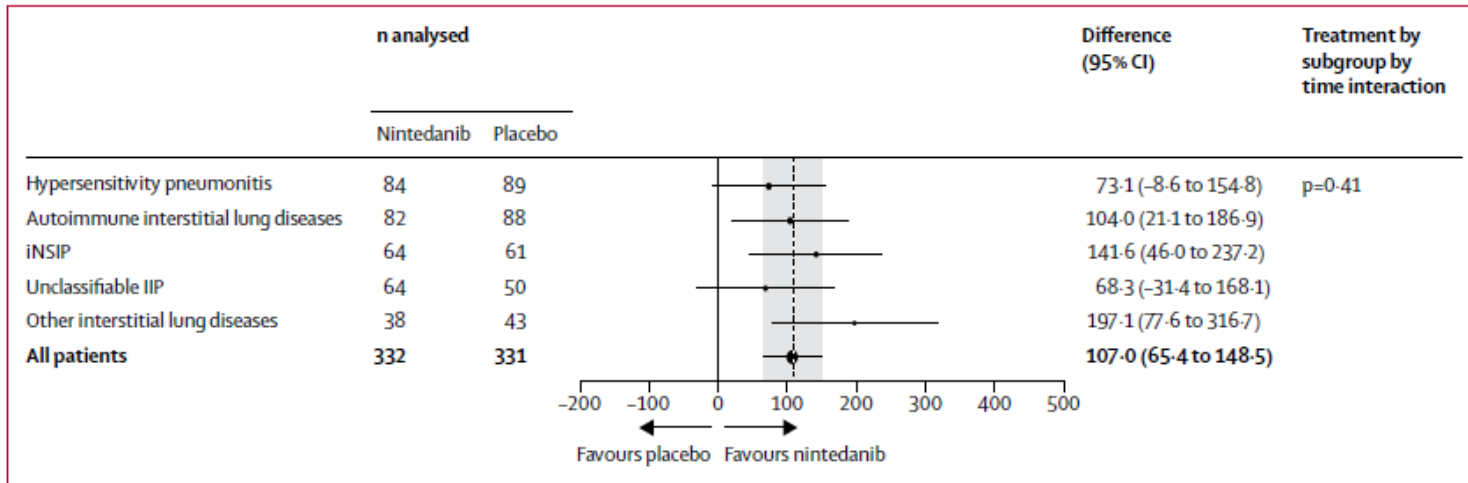


Figure 2: Annual rate of decline in forced vital capacity (mL/year) in five groups by interstitial lung disease diagnosis (overall population)
 iNSIP=idiopathic non-specific interstitial pneumonia. IIP=idiopathic interstitial pneumonia. Other interstitial lung diseases (ILDs)=sarcoidosis, exposure-related ILDs and other terms in the other fibrosing ILDs category.

- The INBUILD trial was not designed for a benefit of nintedanib in specific diagnostic subgroups.
- The results suggest that nintedanib reduces the rate of ILD progression, as measured by FVC decline, in patients who have a chronic fibrosing ILD and progressive phenotype, irrespective of the underlying ILD diagnosis.



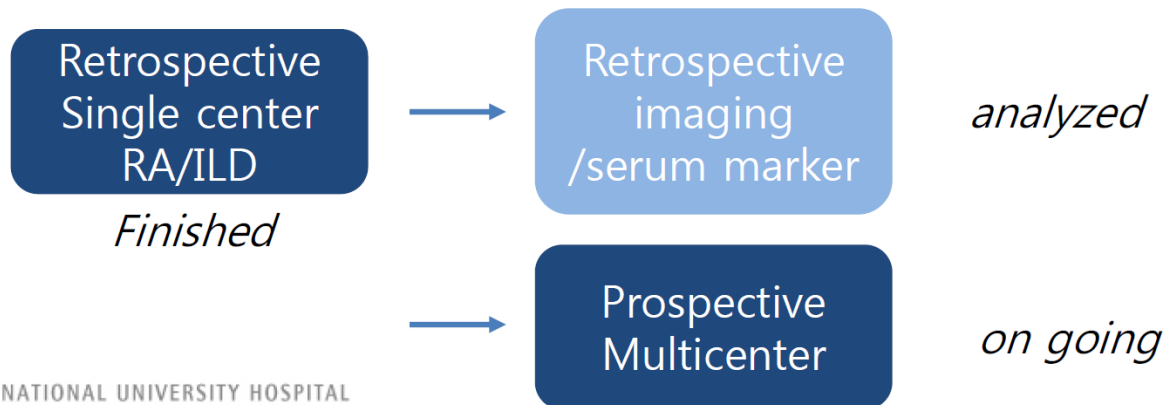
Prognosis

- ILD: 2nd cause of mortality in RA
- ILD contributed to death in 6.8% of females and 9.8% of males in RA
- Risk factors
 - advanced age
 - male sex
 - UIP pattern
 - extent of fibrosis on imaging or histopathology
 - low DLCO



Need of prospective study – *KORAIL cohort*

- Purpose of research: What we want to know...
 - 1) **Clinical course**
 - Are ILDs of RA patients not as severe as systemic sclerosis?
 - 2) **Prediction of prognosis**
 - How can we predict the subgroup of RA-ILD with rapid progression?
 - 3) **Influence of conventional DMARDs or biologic agents for RA on ILD**
 - Which one is more safe for RA patients with ILD?



RA-ILD cohort in Korea (KORAIL)

- **Multicenter, Prospective cohort**
 - 6 centers in Korea
 - target: 150-200 patients with RA-ILD
 - Follow-up period: 3 years
 - Follow-up frequency: every year
 - HRCT, PFT including DLCO, 6-min walk test, DAS28, Bone X-ray, and EDTA/Serum blood samples for each point

- **Organizations**
 - SNUH (Eun Young Lee)
 - SNUH Bundang (Eun Ha Kang)
 - Yeonsei University (Yong-Beom Park)
 - Daegu Catholic University (Jung-Yoon Choe)
 - Suncheonhyang University (Seong Hae Jang)
 - Kyunghee University (Yeon Ah Lee)



KORAIL cohort –Demographics-

Characteristics	Total
No. of patients	163
Age at enrollment (year), mean±SD	66.4±8.1
≥65, n (%)	96 (58.9)
≥70, n (%)	57 (35.0)
≥75, n (%)	23 (14.1)
Gender, n (%)	
Male	54 (33.1)
Female	109 (66.9)
RA Duration (yr), median (range, IQR)	5.9 (0.0 - 42.0, 9.3)
mean±SD	7.6±8.0
ILD Duration (CT dx) (yr), median (range, IQR)	1.6 (0.0 - 16.5, 4.3)
mean±SD	2.7±3.1
BMI, mean±SD	23.7±3.2
Smoking, n (%)	
Never smoking	119 (73.0)
Ex-smoking	28 (17.2)
pack-years, median (range, IQR)	30.0 (10.0 - 50.0, 17.5)
Current smoking	15 (9.2)
pack-years, median (range, IQR)	24.0 (1.0 - 55.0, 14.0)
Unknown	1 (0.6)

Characteristics	Total
RA medication at enrollment	
Methotrexate, n (%)	100 (61.3)
Glucocorticoid, n (%)	160 (98.2)
biologic DMARDs, n (%)	60 (36.8)
RF positive, n (%)	143 (87.7)
titer, mean±SD	279.5±513.6
median (range, IQR)	124.0 (15.0 - 3660.0, 213.0)
Anti-CCP positive*, n (%)	154 (94.5)
≥200	76 (52.4)
titer, mean±SD	279.8±266.7
median (range, IQR)	217.0 (0.4 - 1104.6, 425.0)
Serum KL-6	
titer, mean±SD	599.5±489.9
median (range, IQR)	427.2 (151.3 - 4181.6, 418.5)

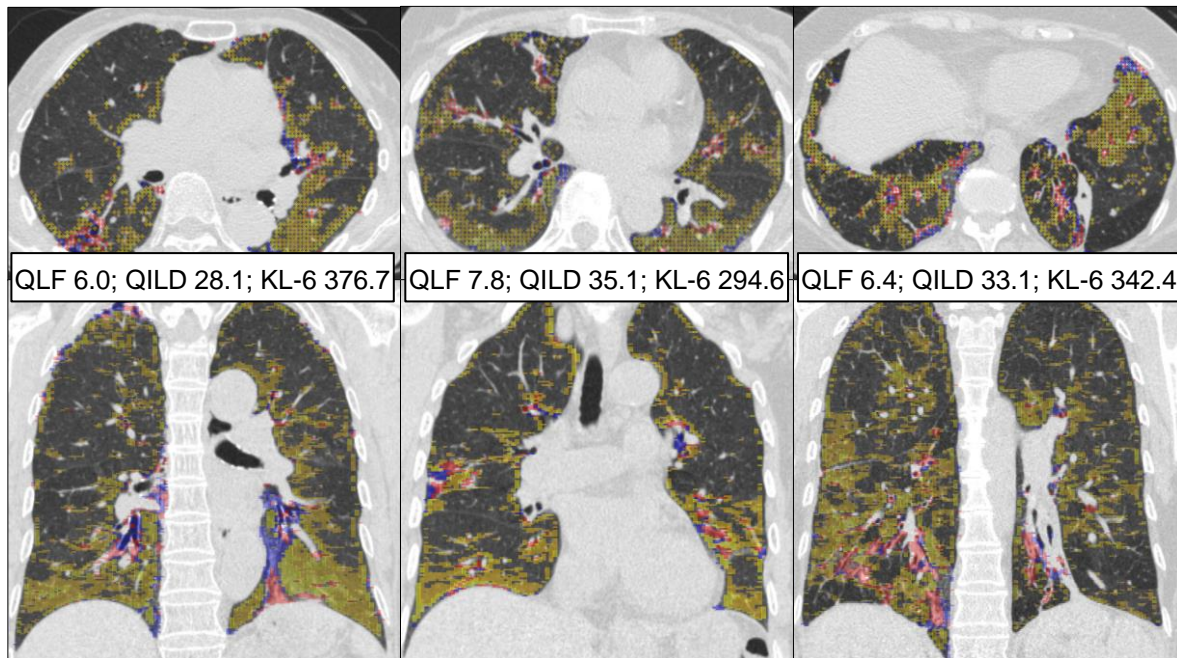


KORAIL cohort

need for precise evaluation of CT change

Quantitative ILD scoring system - computer aided method

A



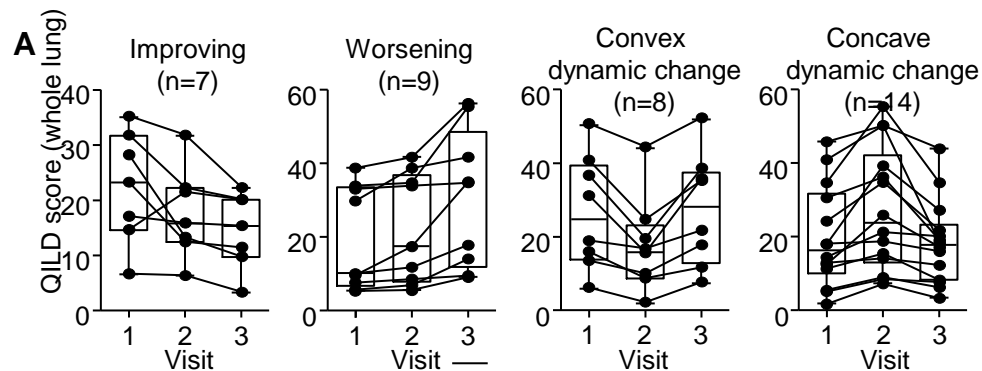
UCLA Center for Computer Vision & Imaging Biomarkers



Jonathan Goldin
MD, Ph.D



Grace Kim
Ph.D



KORAIL cohort

Lung function trajectory

Rheumatology, 2023, 32, 1-11
<https://doi.org/10.1093/rheumatology/kzad007>
 Advance access publication 19 January 2023
 Original article



British Society for
 RHEUMATOLOGY



Rheumatology, 2023, 32, 1-11
<https://doi.org/10.1093/rheumatology/kzad007>
 Advance access publication 19 January 2023
 Original article



British Society for
 RHEUMATOLOGY



Clinical science

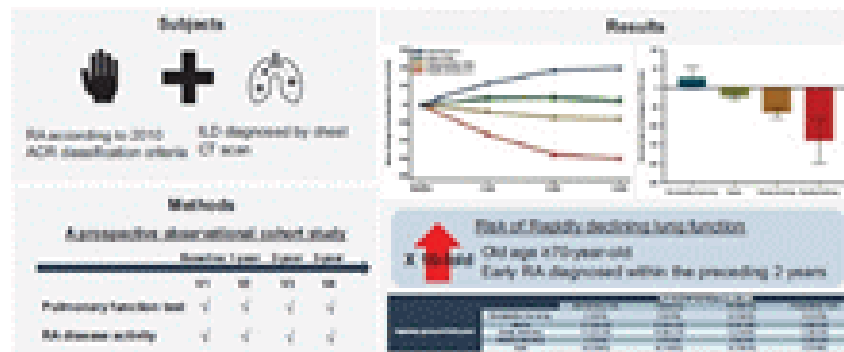
Lung function trajectory of rheumatoid arthritis-associated interstitial lung disease

Sung-Wan Chung^{1,2}, Ji-Sung Lee^{3,4}, You-Jung Ha⁵, Min-Uk Kim⁶, Chan-Ho Park⁷, Jong-Seok Lee⁸, Ji-Won Kim^{9,10}, Sang-Wan Chung¹¹, Jung-Yoon Park¹², Sung-Won Lee¹³, Eun-Ha Kang¹⁴, Yeon-Ah Lee¹⁵, Young-Bum Park¹⁶, Jung-Hoon Choi¹⁷, **Eun-Young Lee¹⁸** for the Korean Rheumatoid Arthritis-Interstitial Lung Disease Cohort Investigators

Clinical science

Methotrexate, leflunomide and tacrolimus use and the progression of rheumatoid arthritis-associated interstitial lung disease

Ji-Won Kim^{9,10}, Sung-Wan Chung¹¹, Jung-Yoon Park¹², Sang-Wan Chung¹³, Min-Uk Kim⁶, Chan-Ho Park⁷, Ji-Sung Lee^{3,4}, Jong-Seok Lee⁸, You-Jung Ha⁵, Eun-Ha Kang¹⁴, Yeon-Ah Lee¹⁵, Young-Bum Park¹⁶, **Eun-Young Lee¹⁸**, Jung-Hoon Choi¹⁷



Future therapy

- Some agents tried to treat IPF
 - antioxidant therapy, pirfenidone, bosentan (no effect)
- rituximab in treatment of DM/PM-ILD, SSc-ILD
 - Initial improvements in pulmonary function in both diseases, further improvements at 2-year follow-up in SSc-ILD
- Abatacept for RA/ILD
 - Some retrospective studies, more evidence needed
- **Nintedanib**
 - Inhibit PDGFR
 - slow down decrease in FVC and improve pt's QOL in IPF and other ILDs
- Lung transplantation
- **Combination or sequential targeted Tx to control the inflammation and fibrosis at proper time may be needed...**



증례

- 56세 여자
- 최근 시행한 검진에서 CPA 이상 소견으로 HRCT 추가로 시행 후 both lower lung에 mild GGO 관찰되어 큰병원 호흡기내과 의뢰되었고, 시행한 혈액검사에서 이상소견 보여 류마티스내과 의뢰
- 계단 오를 때 약간 숨이 찬 정도의 증상과 마른 기침
- FANA(+, 1:40), anti CCP(+) 52, ANCA(-), ESR 25, CRP 0.01
- 신체검진에서는 BT 정상, arthritis, rash 등 없음
- 다음 단계는?

