Pulmonary Involvement in Rheumatic Diseases:Review

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Financial disclosures

- Up to Date (writer)
- Genentech (formerly ILD clinical investigator)
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- Boehringer Ingelheim (unpaid advisory board)
- FDA Advisory Committee

Summary Slide

- ILD associated with CTD can have a mortality that rivals IPF
- Risk factors for ILD in different population of CTD are identifiable
- Inflammatory disease can be treated with anti-inflammatory agent and emerging data suggests that fibrotic disease may be amenable to treatments employed in IPF
- Early identification of those at risk and frequent monitoring is important to avoid progression of disease and missed opportunity for treatment, clinical trials and if needed lung transplant.

Outline

- Overview of CTD and ILD
- Rheumatoid arthritis: risk factors for ILD , other lung manifestations in RA and recent trial results.
- Scleroderma: risk factors for ILD recent clinical trials
- Inflammatory myositis: risk factors for ILD and treatment options
- Interstitial pneumonia with autoimmune features (IPAF)
- Screening and treatment strategies in CTD-ILD

Clinical scenarios you will be asked to comment on:

- Patient with ILD seen in pulmonary, does this patient have a CTD.
- Patient with known CTD now with ILD and declining
- Patient you meet with CTD and you are wondering or asked , “ do they have ILD or are they are at higher risk for it”

Antibodies and clinical correlation

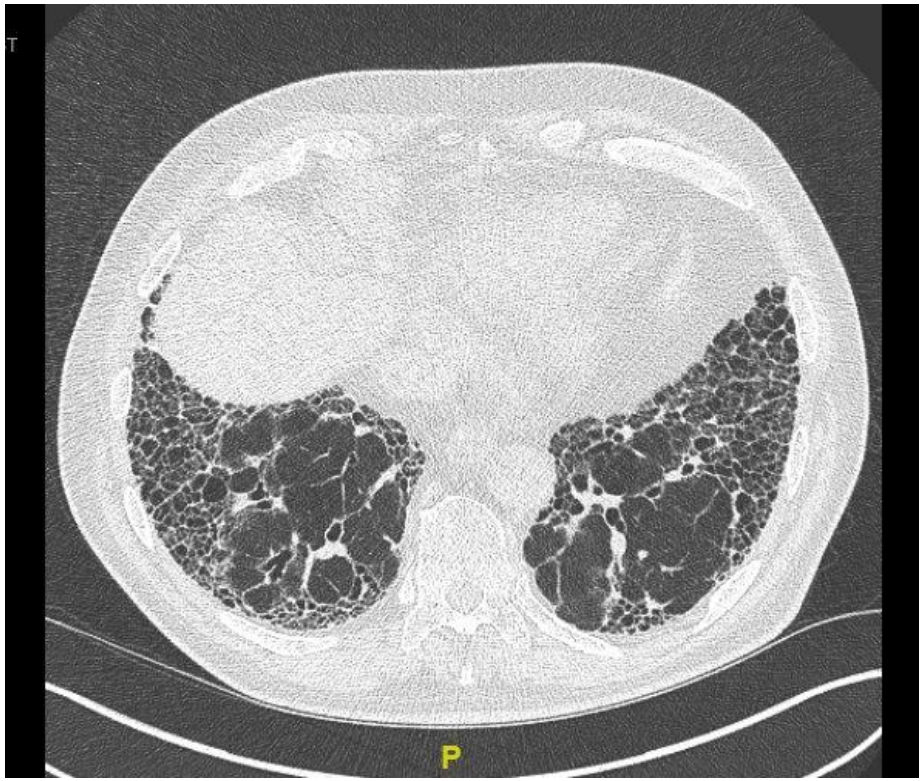
- ANA: SLE, SS, Sjogrens, viral, bacterial infection, hepatitis, false + common
- Centromere: limited scleroderma, less likely ILD, more likely PAH
- **Ro**:Sjogrens (50%),discoid lupus, scleroderma like syndromes, antisynthetase syndrome (ASSD)
- **Scl-70:** diffuse scleroderma but seen only in 20% SSc : **higher risk of ILD**
- **RNP;** can have different diseases, often akin to scleroderma or myositis, **high risk of ILD and PAH**
- **Ds DNA**: seen in SLE and may correlate with renal disease: we have seen false + in low titer, **rarely correlates with ILD**
- Other ab : antisynthetase (Jo-1, pl-12 pl-7) , MDA 5 , Th/To U3 RNP. Major clinical feature with these is ILD. Cytoplasmic staining (seen in ASSD)

The value of the myositis panel in ILD assessment

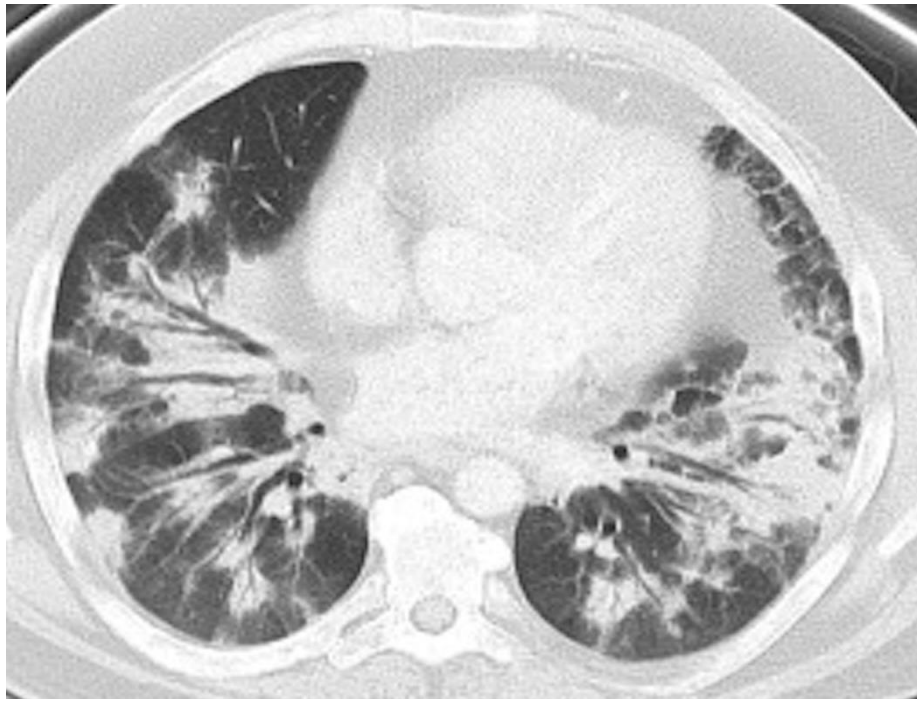
MYOSITIS PANEL				Other Antibodies	
Myositis-Specific		Myositis-Associated			
Anti-Synthetases					
JO-1	NEG	PM-SCL	NEG	P155/140	NA
PL-7	NEG	KU	NEG	RNA POL	NA
PL-12	NEG	U1RNP	NEG	TH/TO	NA
EJ	NEG	U2RNP	NEG	U3RNP	NA
OJ	NEG	RO60	IND	MJ	NA
				MDA5	NA
MI-2	NEG				
SRP	NEG			OTHER ANALYTES	NA

UIP clearly has the highest mortality

Honeycombing and traction bronchiectasis c/w UIP(specifc but not sensitive): seen in IPF and ILD-CTD and in 60% of RA-ILD, rarely in ANCA+



Consolidation and GGO most c/w inflammatory disease (like in antisynthetase syndrome or OP/NSIP in CTD)



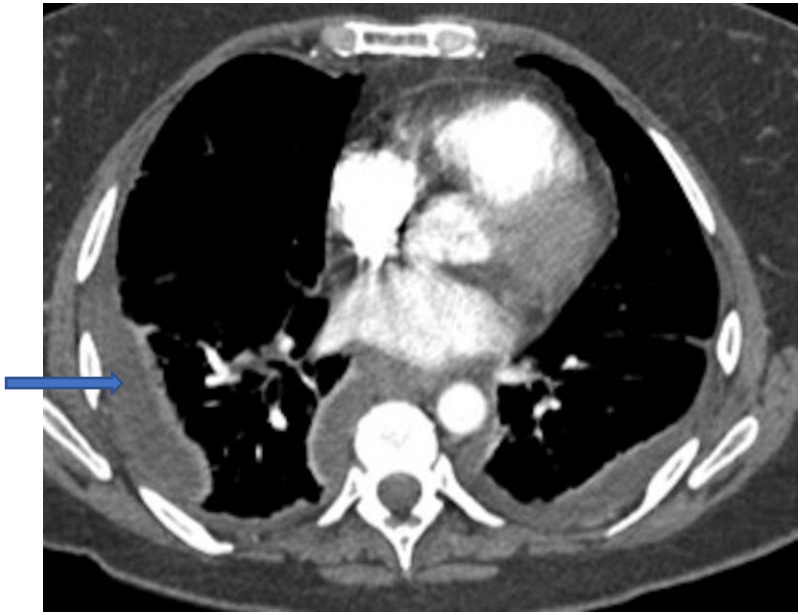
ILD in the CTD: a new paradigm and implications for treatment

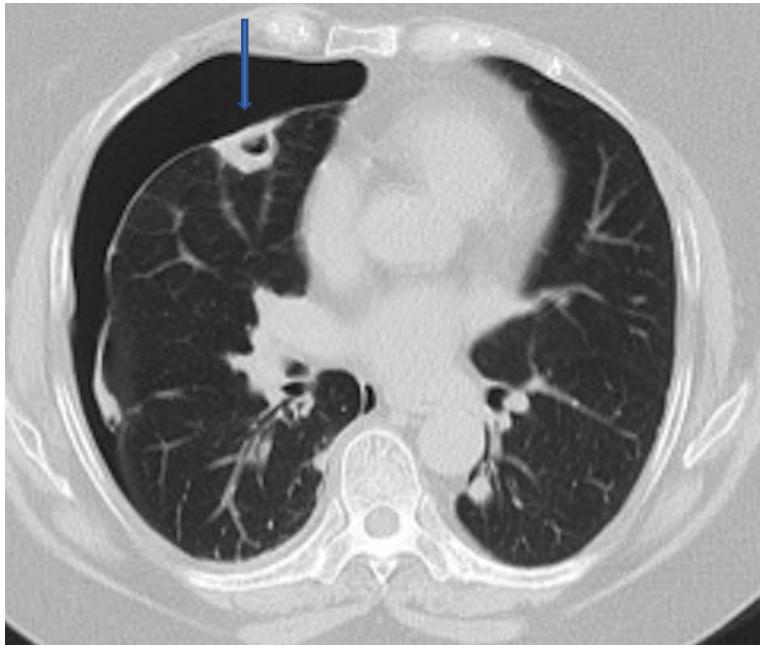
- When the predominant lung lesion is inflammatory, then anti-inflammatory therapy is indicated
- When the predominant lung lesion is fibrotic, then anti fibrotic therapies are indicated
- Will some patients benefit from both treatments?
- What are the costs ? (they are high)

Rheumatoid Arthritis and the Lung: classic ILD CTD with multicompartmental disease

- ***Clinically significant interstitial lung disease occurs in 5-10% (UIP, NSIP, LIP).***
- Airway: Obstructive bronchiolitis (poor), Follicular bronchiolitis (better prognosis)
- Cryptogenic organizing pneumonia(better prognosis)
- Pleural effusion/sterile empyema
- Emphysema**
- Bronchiectasis
- Nodulosis
- Upper airway obstruction
- Methotrexate and other drug toxicity (.3%)

A word about Pleural disease and Rheumatoid nodules



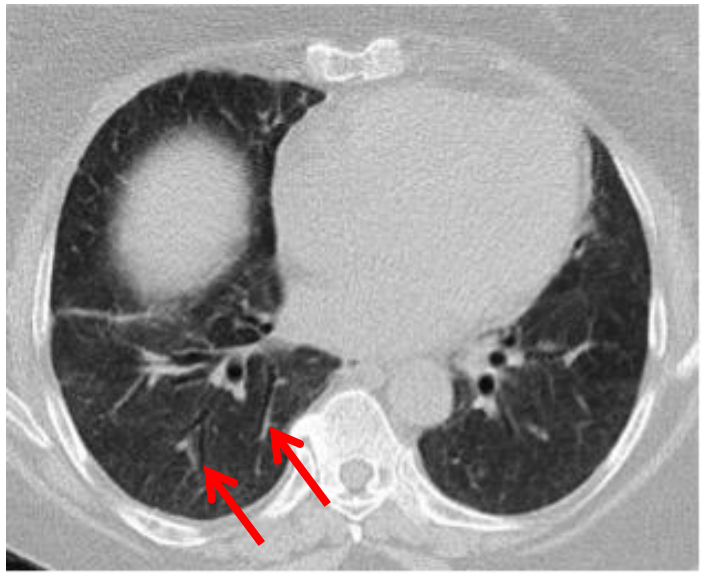


Just a word on Airway Disease in RA

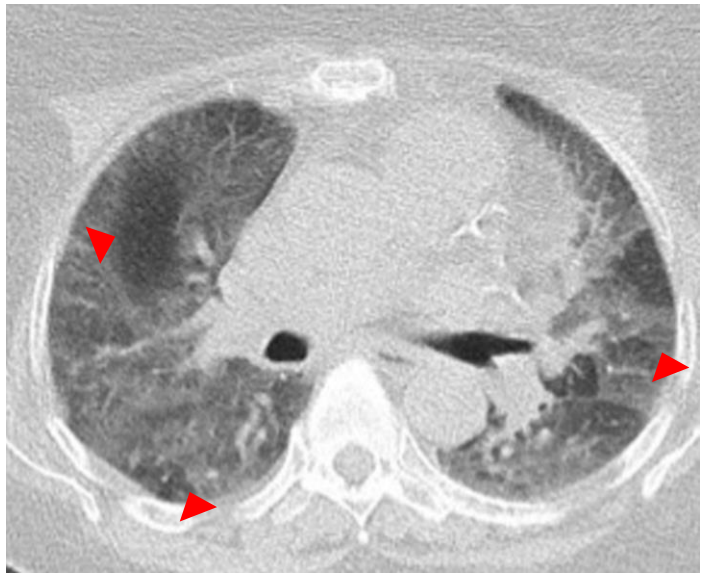
- Airway disease with predominantly obstruction on PFTs (FEV1<70%, ratio FEV1/FVC<) is not uncommon
- May mimic asthma
- mosaicism or air trapping on CT is common
- Some types of bronchiolitis are potentially treatable (like follicular bronchiolitis) though OB (obliterative bronchiolitis) is often not treatable and requires referral for transplant.
- Emphysema is common in RA, many of our pts smoke or did smoke, which can complicate attempts at treatment and clinical trials

Airway thickening Panel A
Air trapping on expiratory views

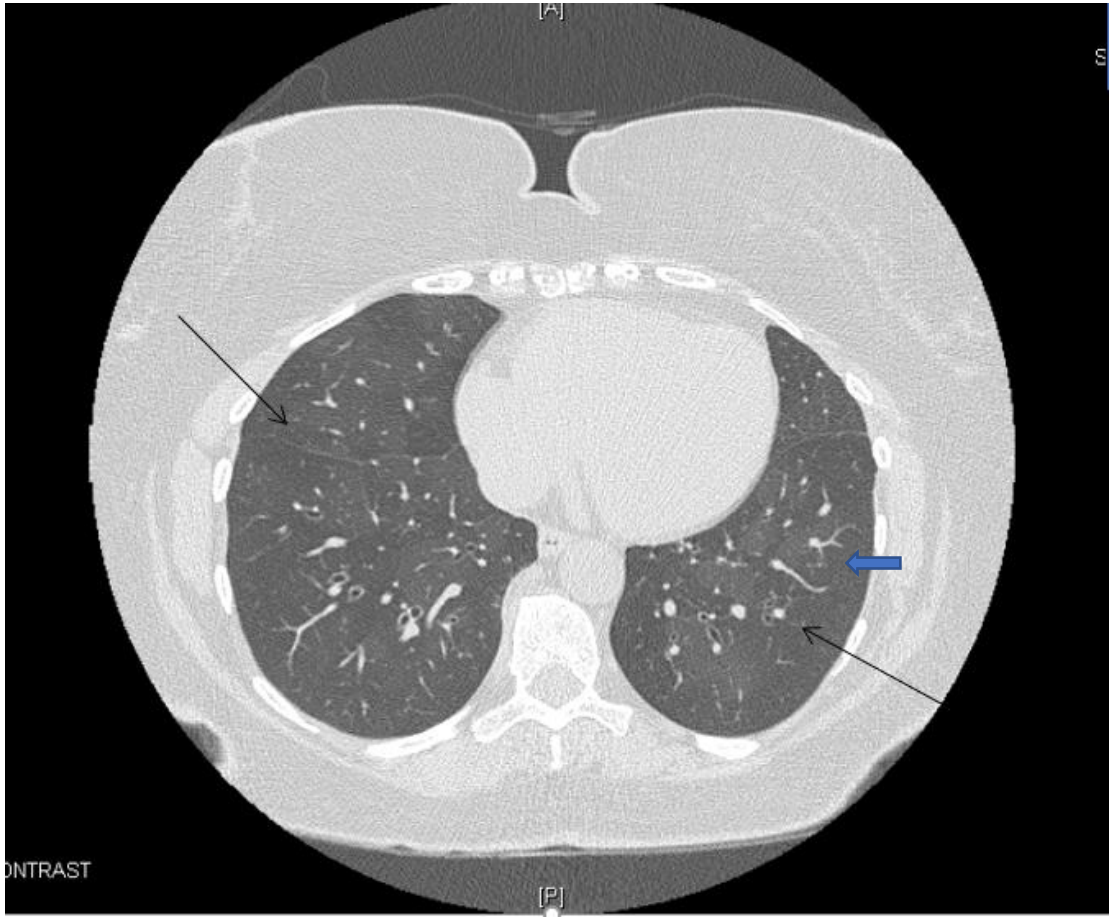
A



B

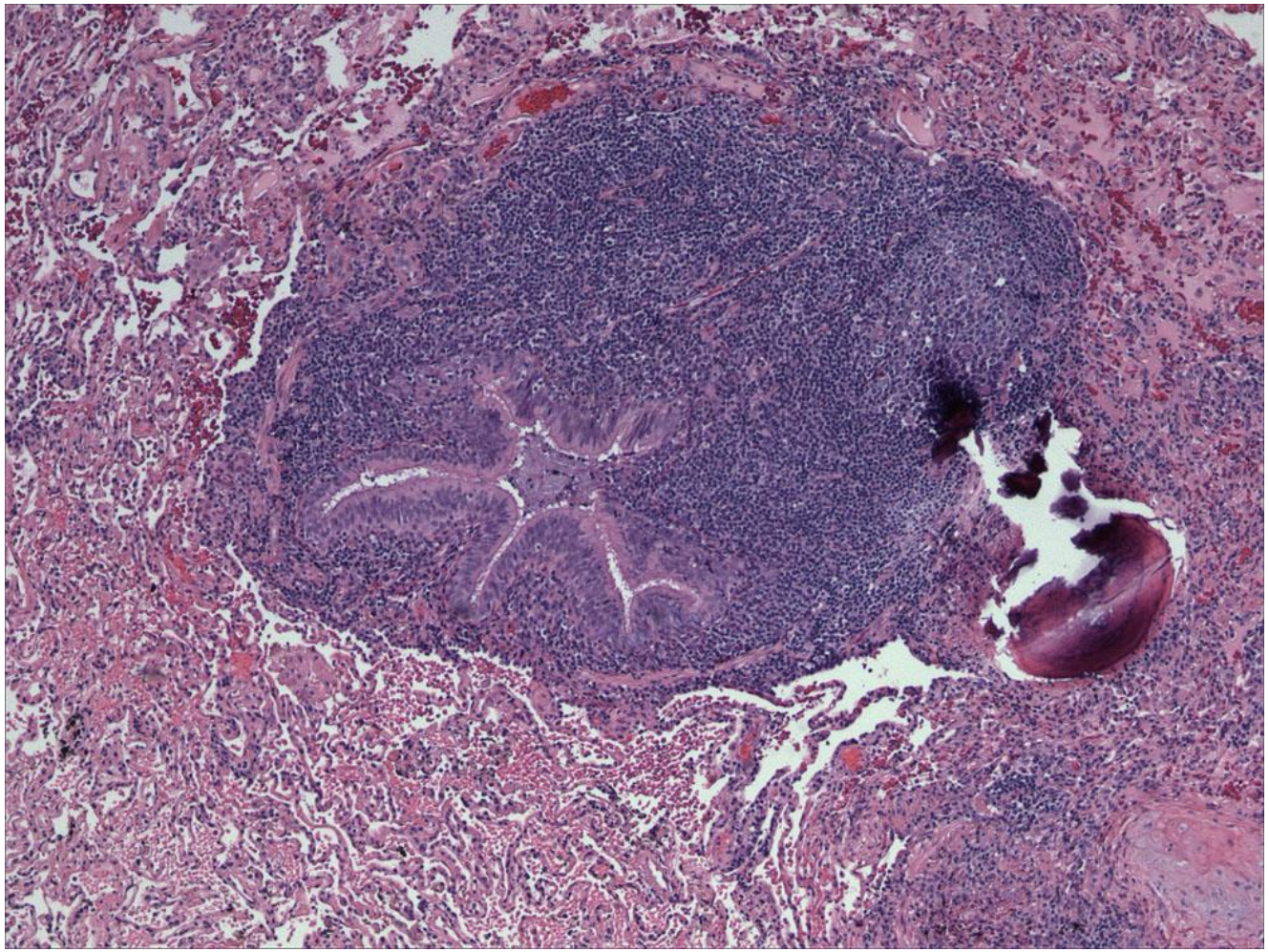


50 yo female with RA CCP + and “asthma”



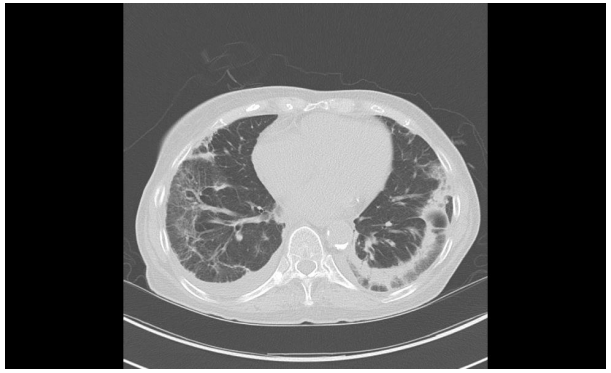
air trapping
on HRCT

Lung biopsy dx: Follicular bronchiolitis



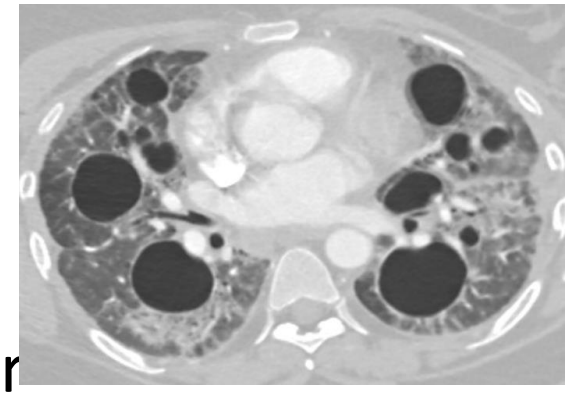
Inflammatory and non fibrotic Lung Disease in RA

Organizing pneumonia (OP)



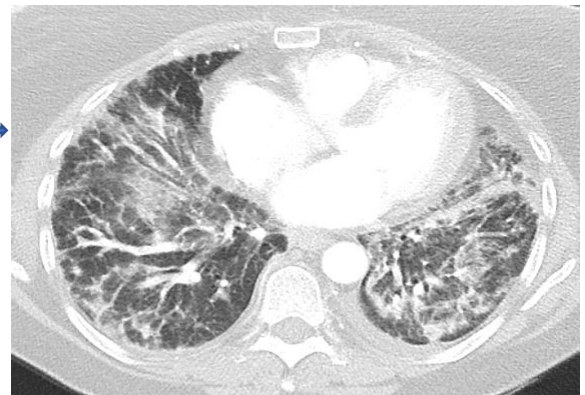
Cellular NSIP

LIP: (lymphocytic interstitial pneumonia)

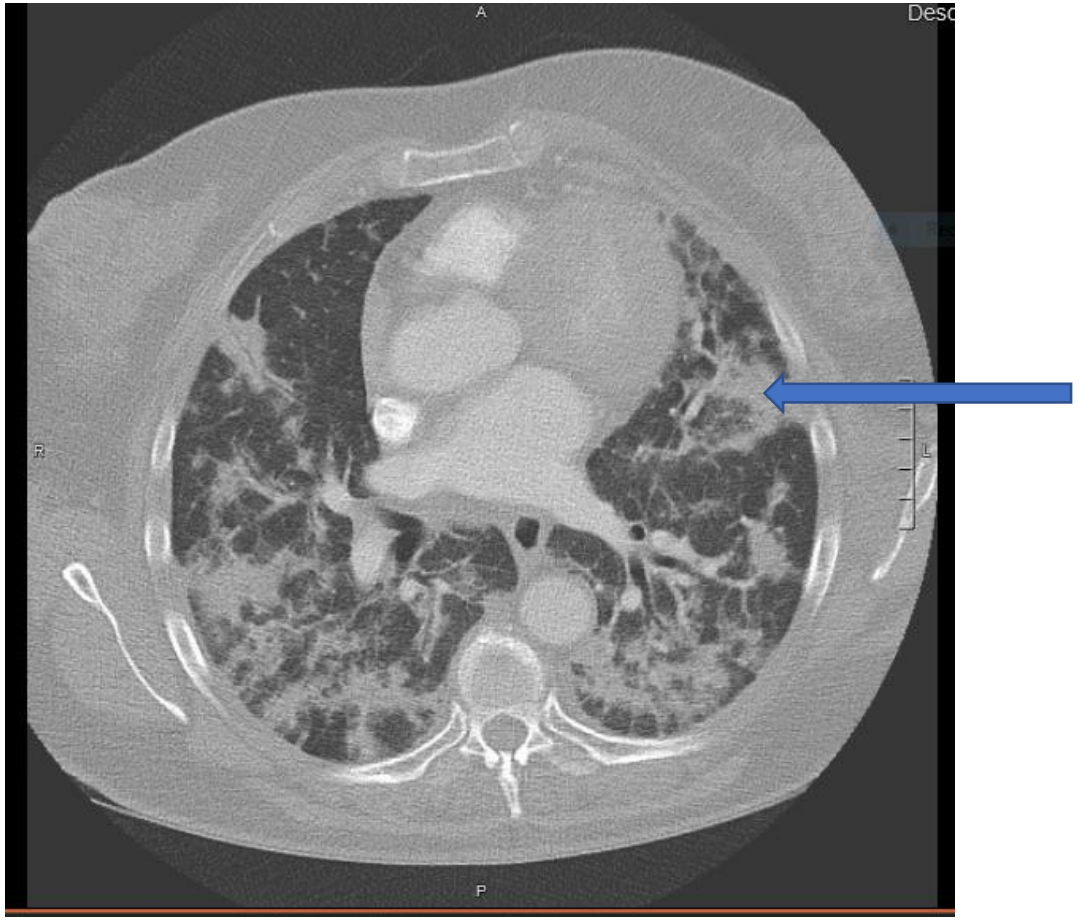


AIP or DAD (diffuse alveolar damage) phenotypes can occur

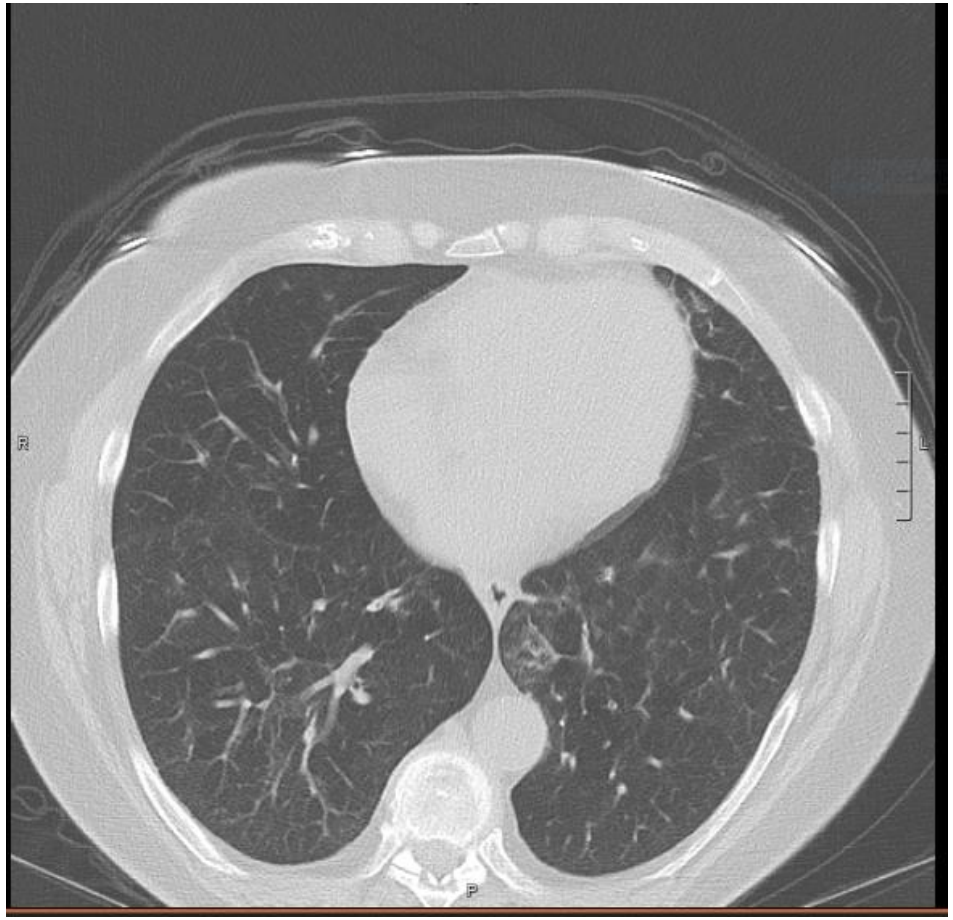
in RA but are uncommon



Case: 60 y.o. female presented to MICU with hypoxemia and new bilateral ankle pain



High Titer RF/CCP ab+. Diagnosed with RA and treated with CS and RTX with excellent result in both lung disease and arthritis



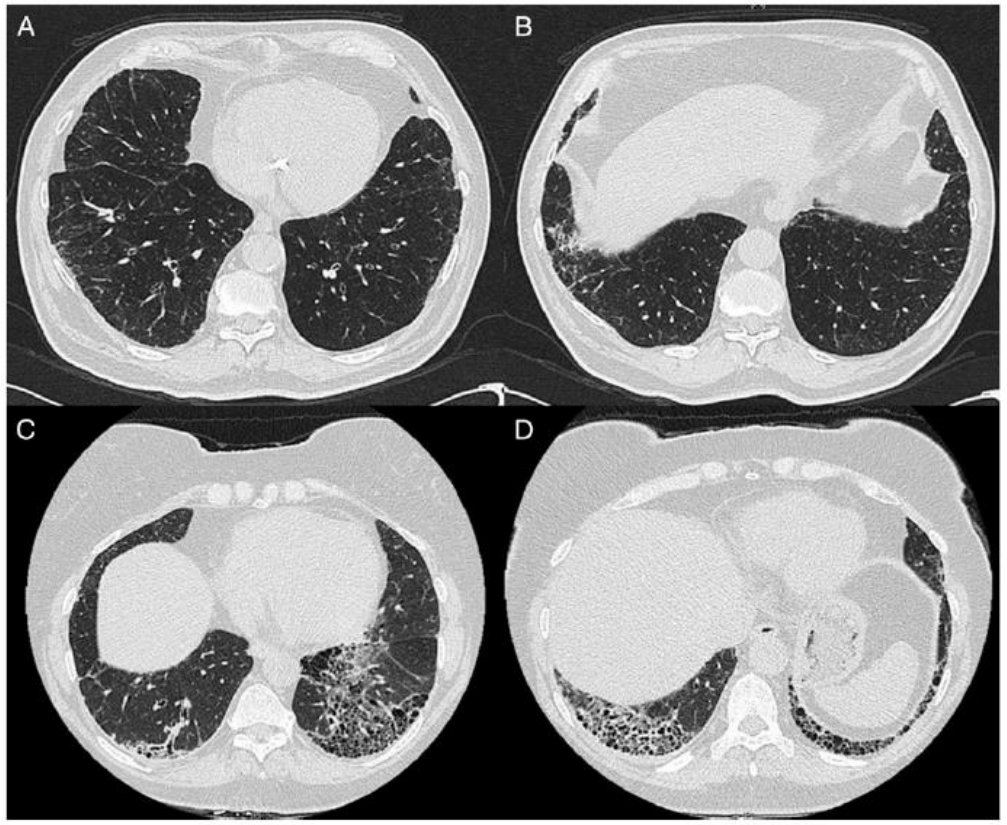
ILD in RA: A spectrum of disease

- **Most common clinical manifestation of lung involvement**

- **10% of individuals with RA have clinically-evident ILD and an additional 30% have subclinical disease**

- **Disease progression was observed in 57% of RA patients with subclinical RA-ILD after a mean length of follow-up of 1.5 years**

- **Up to 65% of individuals have UIP pattern**



Gochuico Arch Int Med 2008
Bongartz Arth Rheum 2010
Olson AJRCCM 2011
Kim Eur Resp J 2010
Doyle Chest 2013, 2014

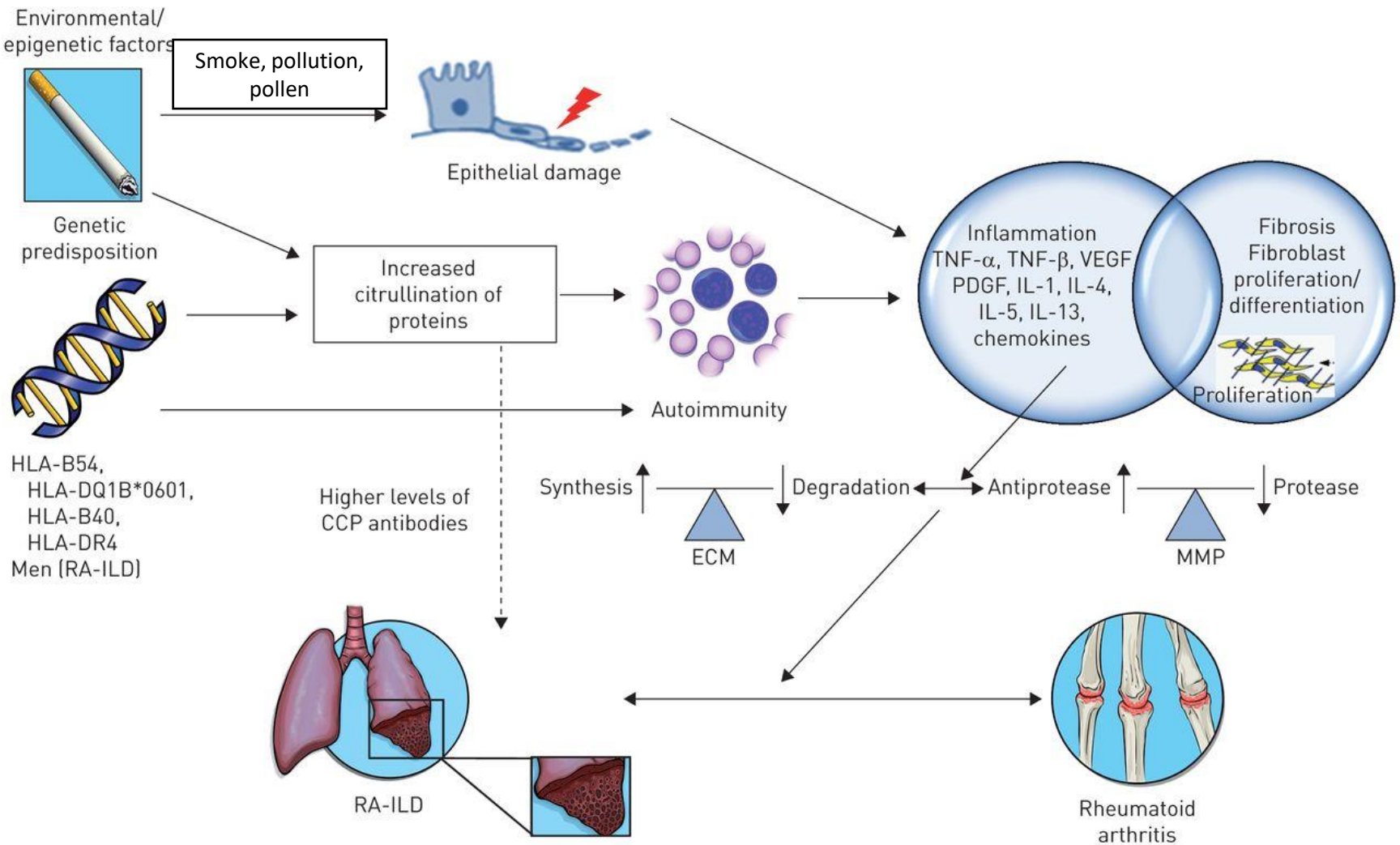
Risk Factors for RA-ILD

- **RA-ILD is associated with:**
  - *Increased age / smoking history/male*
  - *Increased RA disease severity*
  - *Increased respiratory symptoms*
  - *Increased RF and anti-CCP levels*
  - *Obesity*

Bimodal Distribution of RA-ILD

- Majority of patients with RA develop ILD >10 years after articular manifestations but when do most pts develop early ILD?
- Minority of patients develop clinically-evident ILD shortly after articular disease
- In some patients, ILD is first manifestation of RA and RA may actually ‘start’ in the lungs
  - Cohort of 74 patients with anti-CCP positivity and lung disease (~50% with ILD) in the absence of existing RA or other connective tissue disease, 3 of whom developed articular disease within 1-2 years

Fischer Respir Med 2012

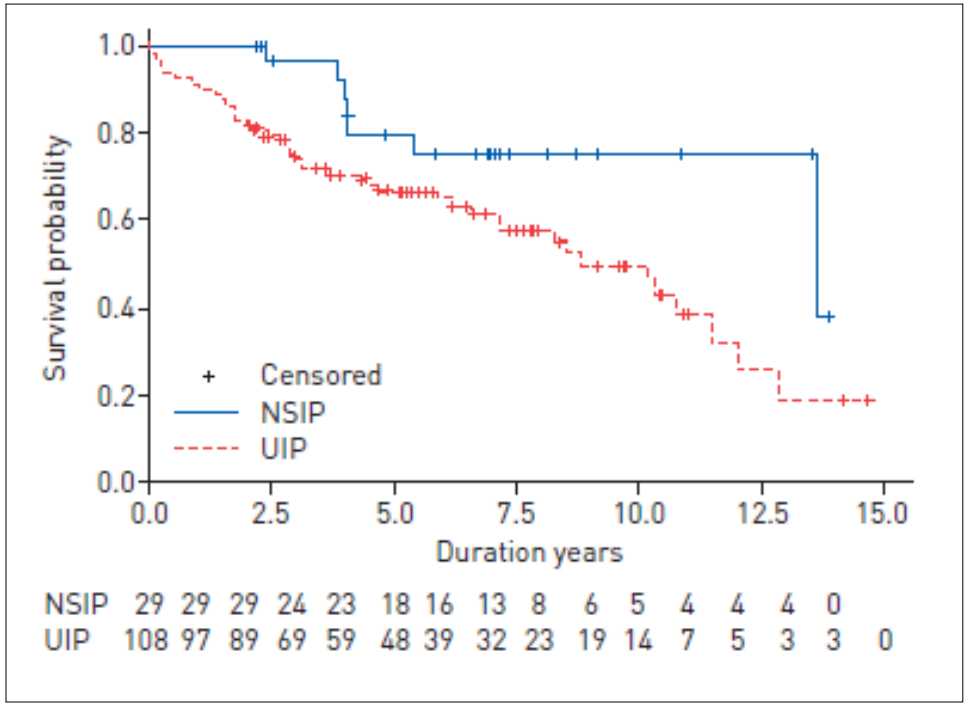


Mortality of RA-ILD

- **While overall mortality rates for RA are declining, death from RA-ILD has increased**

- **Survival in RA-UIP resembles that of IPF**

- ***In a model controlling for age, sex, smoking and HRCT pattern, a lower baseline FVC % pred and a 10% decline in FVC % pred from baseline to any time during follow up were independently associated with an increased risk of death.***



Solomon ERJ 2016

IPF and RA ILD: A spectrum of ILD?
MUC5B in IPF

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Common *MUC5B* Promoter Polymorphism and Pulmonary Fibrosis

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Tasha E. Fingerlin, Ph.D., Weiming Zhang, Ph.D.,
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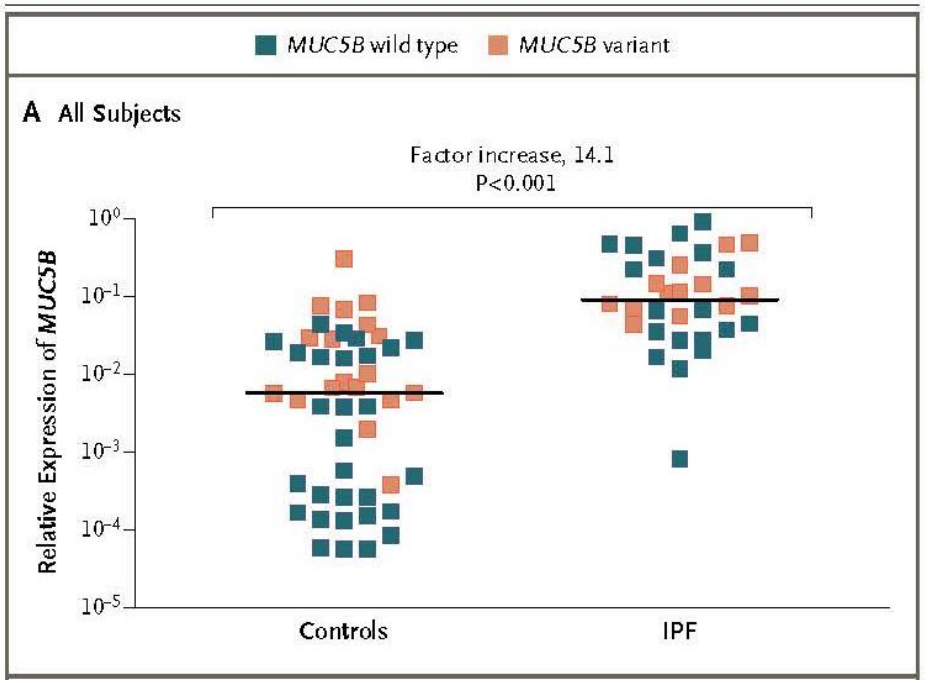
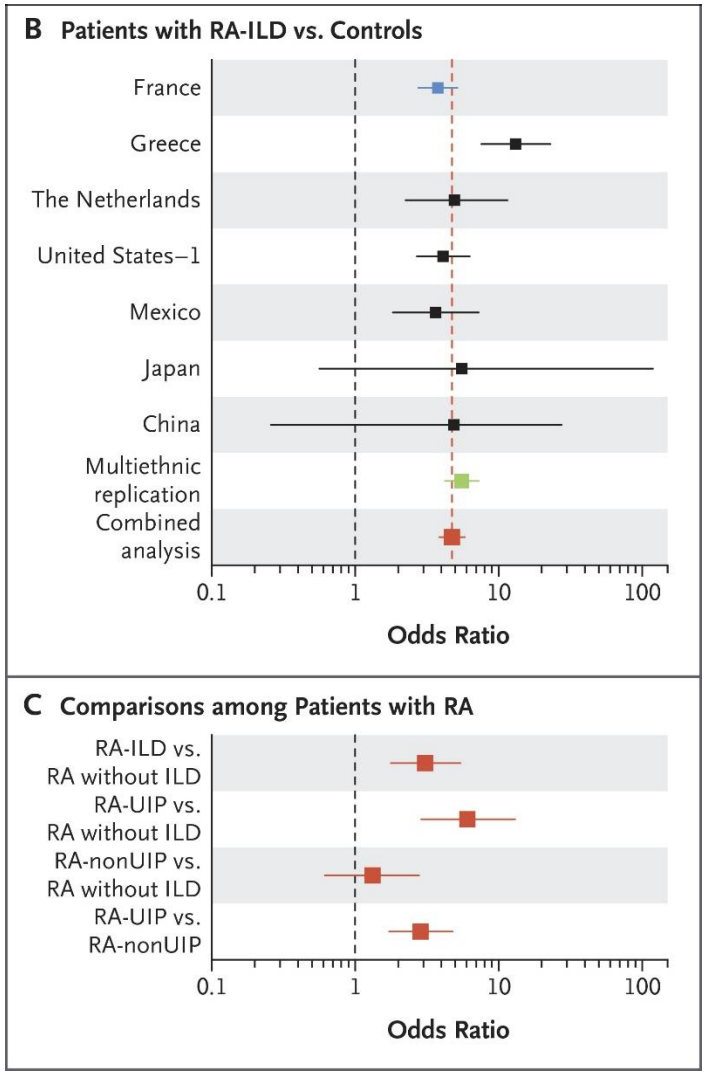
Kenneth B. Adler, Ph.D., Burton F. Dickey, M.D., Roland M. du Bois, M.D.,
Ivana V. Yang, Ph.D., Aretha Herron, B.A., Dolly Kervitsky, B.A., Janet L. Talbert, M.S.,
Cheryl Markin, B.A., Joungjoa Park, B.A., Anne L. Crews, B.A., Susan H. Slifer, Ph.D.,
Scott Auerbach, Ph.D., Michelle G. Roy, B.A., Jia Lin, B.A., Corinne E. Hennessy, M.S.,
Marvin I. Schwarz, M.D., and David A. Schwartz, M.D.



MUC5B in RA-ILD



- Patients with RA-ILD demonstrated over-representation of the *MUC5B* promoter variant rs35705950 compared to RA patients without ILD.
- Stronger associations in RA-UIP vs. RA-nonUIP.

Juge NEJM 2018

Similarities of RA UIP and UIP/IPF

- Similar demographics (male, older, smokers)
- Somewhat similar decline in lung function
- Excess of mutations in genes that were previously linked to familial interstitial pneumonia, including *TERT*, *RTEL1*, *PARN*, and *SFTPC*.
- MUC5B genetic variant in RA ILD similar to what is seen in IPF (NEJM 2019)

GAP tool in RA ILD (Morisette J et al Resp Med 2017, Ley et al Ann Int Med 2012)

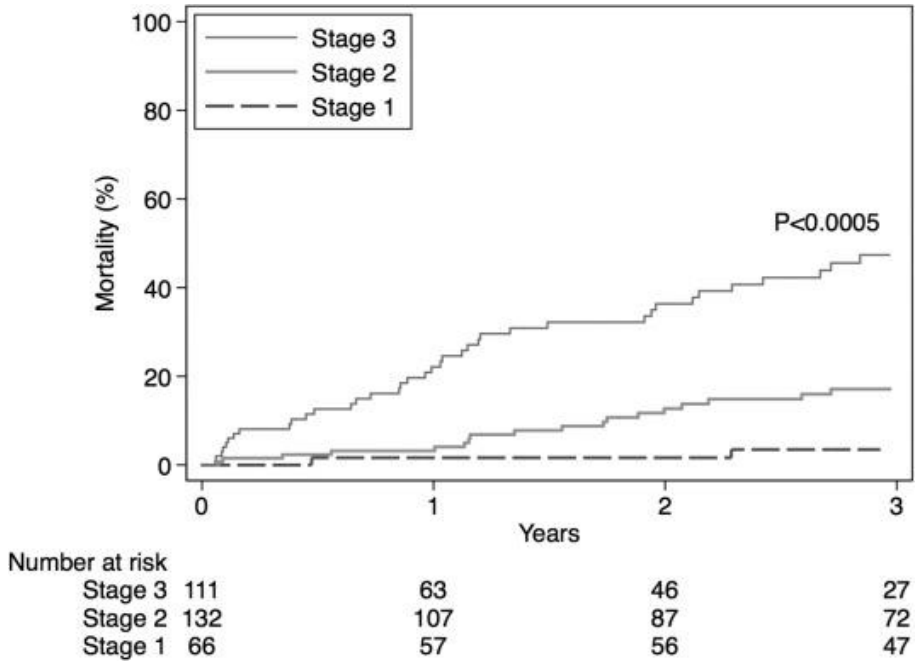


Figure 2. **The GAP index and staging system.**

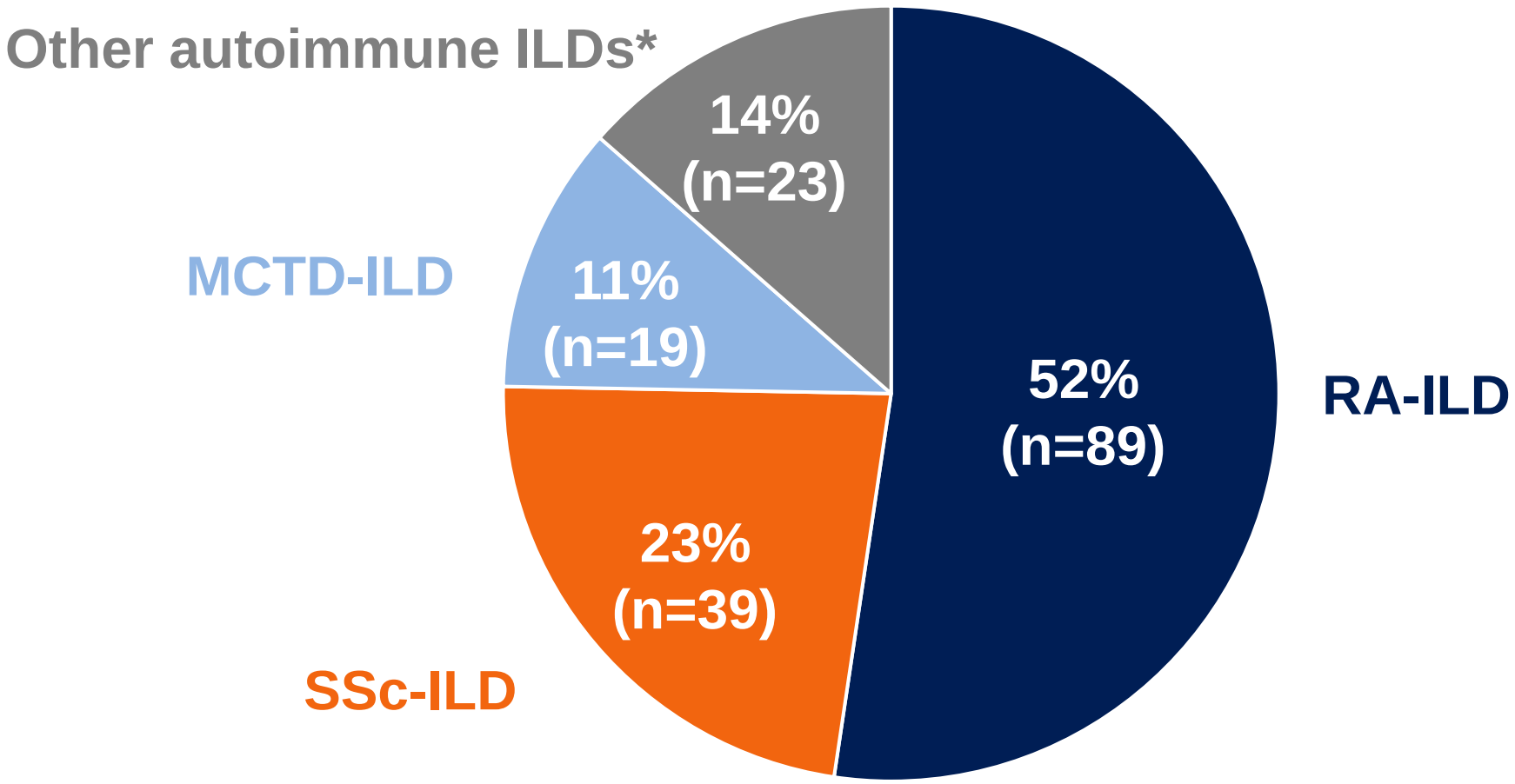
	Predictor	Points
G	Gender	
	Female	0
	Male	1
A	Age, y	
	≤60	0
	61–65	1
	>65	2
P	Physiology	
	FVC, % *predicted*	
	>75	0
	50–75	1
	<50	2
	DLCO, % *predicted*	
	>55	0
	36–55	1
	≤35	2
	Cannot perform	3
	Total Possible Points	8

Stage	I	II	III
Points	0–3	4–5	6–8
Mortality			
1-y	5.6	16.2	39.2
2-y	10.9	29.9	62.1
3-y	16.3	42.1	76.8

What about anti-fibrotic therapy in RA ILD?

- Pirfenidone
- Nintedinab
- Both FDA approved in IPF

RA ILD Treatment: the INBUILD trial (Nintedinab)

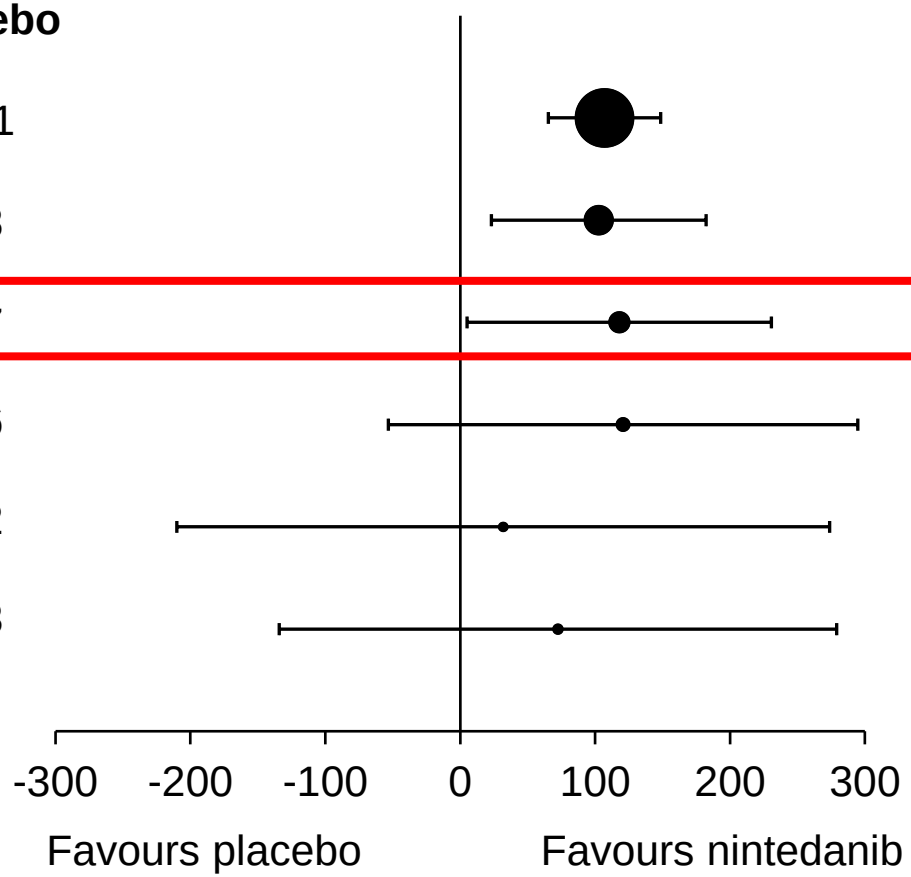


*Subjects with an autoimmune disease noted in the “Other fibrosing ILDs” category of the case report form, including Sjogren’s disease-related ILD, IPAF, and undifferentiated autoimmune disease-related ILD. IPAF, interstitial pneumonia with autoimmune features. MCTD, mixed connective tissue disease.

Matteson EL et al. Poster presented at American College of Rheumatology Convergence Conference 2020.
https://www.usscicomms.com/respiratory/ACR2020/matteson

INBUILD: Difference in rate of decline in FVC (mL/year) over 52 weeks with nintedanib vs placebo by diagnosis: **similar to IPF trials**

	N analysed		Difference in rate of decline in FVC (95% CI)
	Nintedanib	Placebo	
All subjects	332	331	107.0 (65.4, 148.5)
Subjects with autoimmune disease-related ILDs	82	88	102.7 (23.2, 182.2)
RA-ILD	42	47	117.9 (5.2, 230.7)
SSc-ILD	23	16	120.7 (-53.2, 294.6)
MCTD-ILD	7	12	31.9 (-210.0, 273.8)
Other fibrosing ILDs	10	13	72.5 (-134.1, 279.0)



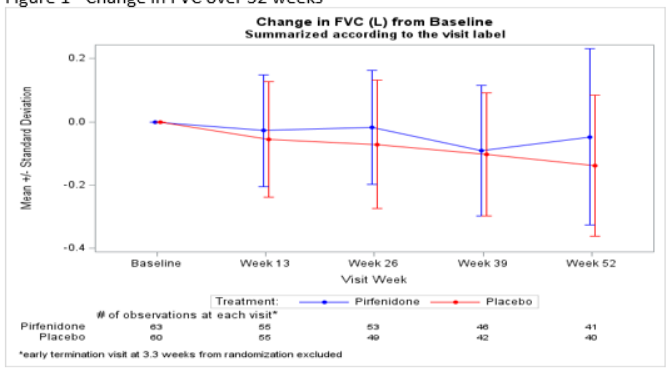
Treatment-by-subgroup-by-time interaction p=0.91

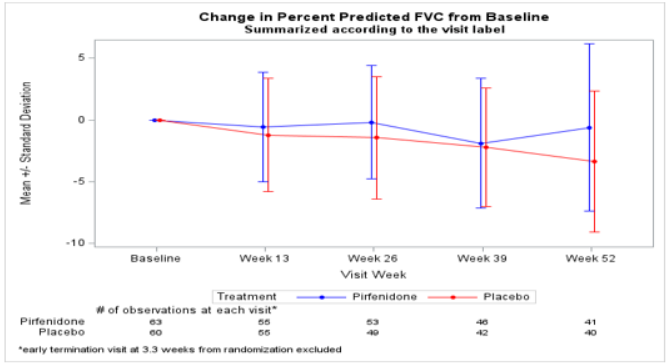
Matteson E et al. Poster presented at American College of Rheumatology/Association for Rheumatology Professionals (ACR/ARP) Annual Meeting 2019. http://ildposters2019.com/pdf/ACR_INBUILDautoimmuneILDs_Matteson.pdf

TRAIL 1:Randomized, Double-Blinded, Placebo-Controlled, Phase 2 Study of Safety, Tolerability and Efficacy of Pirfenidone in Patients with Rheumatoid Arthritis Interstitial Lung Disease (Solomon JJ et al ACR Nov 2021) CLOSED EARLY and UNDERPOWERED !!

Table. Key Secondary Endpoints			
End Point	Pirfenidone (N=63)	Placebo (N=60)	P-value
Decline in FVC at 52 wk - ml/yr			
Overall Population	-66 ± 21	-146 ± 21	0.0082
Patients with UIP pattern on HRCT	-43 ± 31	-169±24	0.0014
Decline in FVC at 52 wk - % predicted			
Overall Population	-1.02 ± 0.51	-3.21 ± 0.52	0.0028
Patients with UIP pattern on HRCT	-0.2 ± 0.74	-3.81 ± 0.70	0.0002

Figure 1 - Change in FVC over 52 weeks



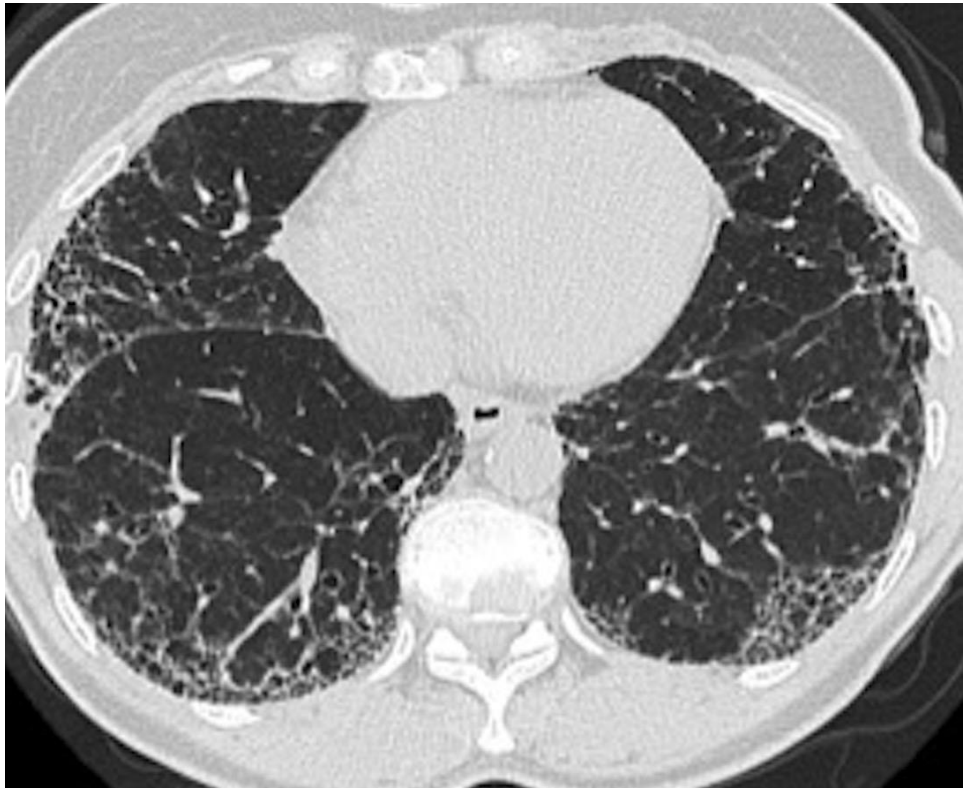


Is there longer term data? Survival and course of lung function in the presence or absence of antifibrotic treatment in patients with **idiopathic pulmonary fibrosis**: long-term results of the INSIGHTS-IPF registry

- 588 ***IPF*** patients: prospective observational cohort
- The one-year and two-year survival rates were 87% *versus* 46% and **62% *versus* 21%,** respectively, for patients with *versus* without antifibrotic therapy
- The risk of death was **37% lower in patients** with antifibrotic therapy (HR=0.63, 95% CI: 0.45, 0.87; p=0.005)
- Overall decline of FVC and DLco was slow and did not differ significantly between patients with or without antifibrotic therapy
- Quality of life issues are not well defined in terms of benefits
- ***Cost analysis*** will be important as well

Behr J et al. Eur Respir J 2020;56:1902279.

Fibrosis Scenario 1: 60 yo with stable RA +CCP on Abatacept: FVC 60% with progressive dyspnea for the past 6 months. Infection and heart disease are excluded. **What would you do?**



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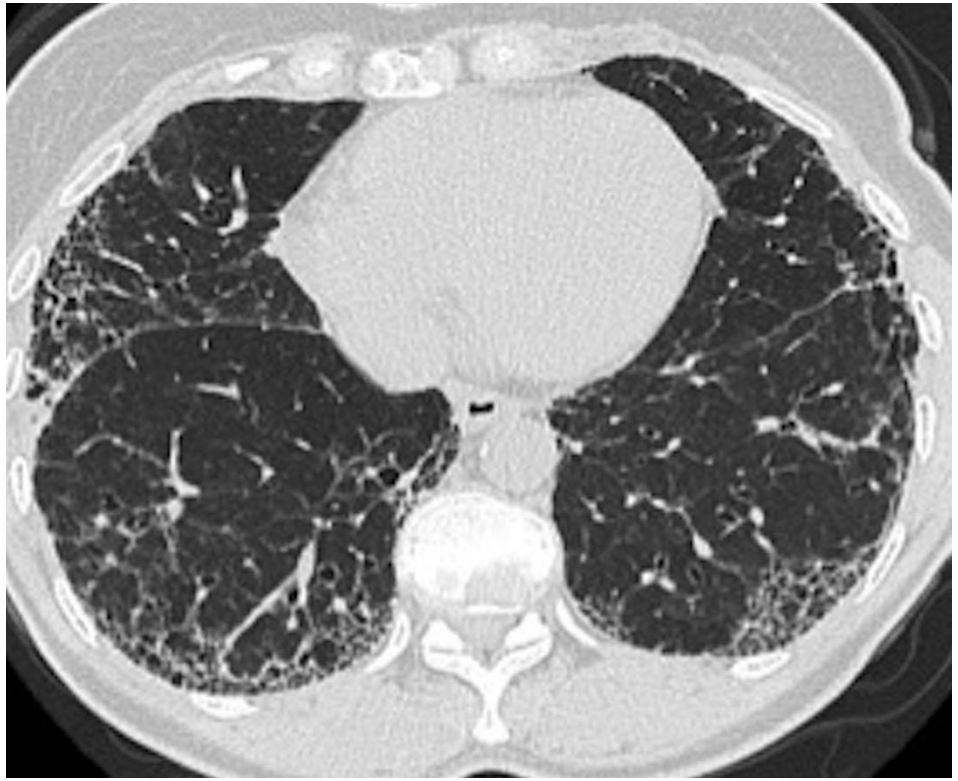
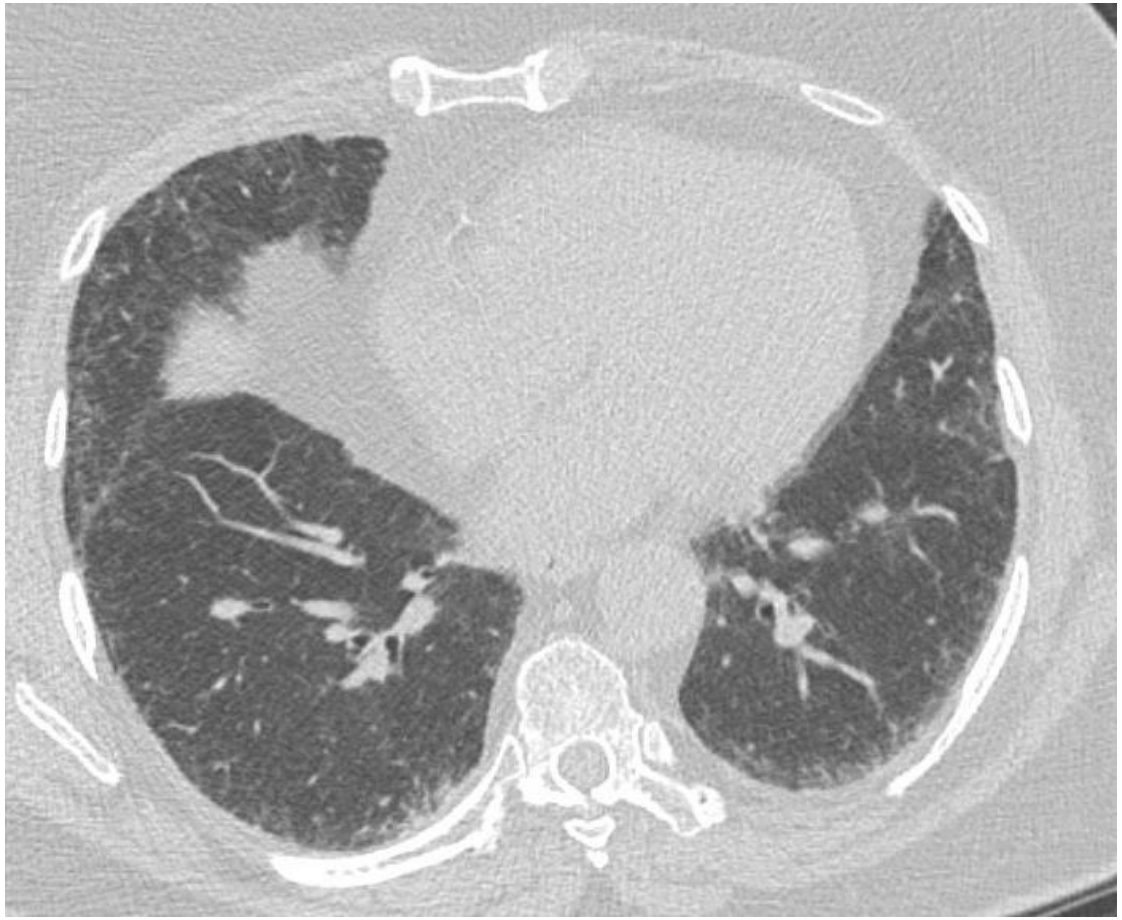


Teaching points :

- Progressive phenotype
- UIP pattern on HRCT
- ***In the year 2022, treat with anti-fibrotic therapy***
- Consider lung transplant evaluation if appropriate

Fibrosis Scenario II: 60 yo RA CCP + former smoker : low dose CT done as part of lung cancer screening, no symptoms and FVC 85% DLCO 72% (first set of PFTs): **what would you do** ?



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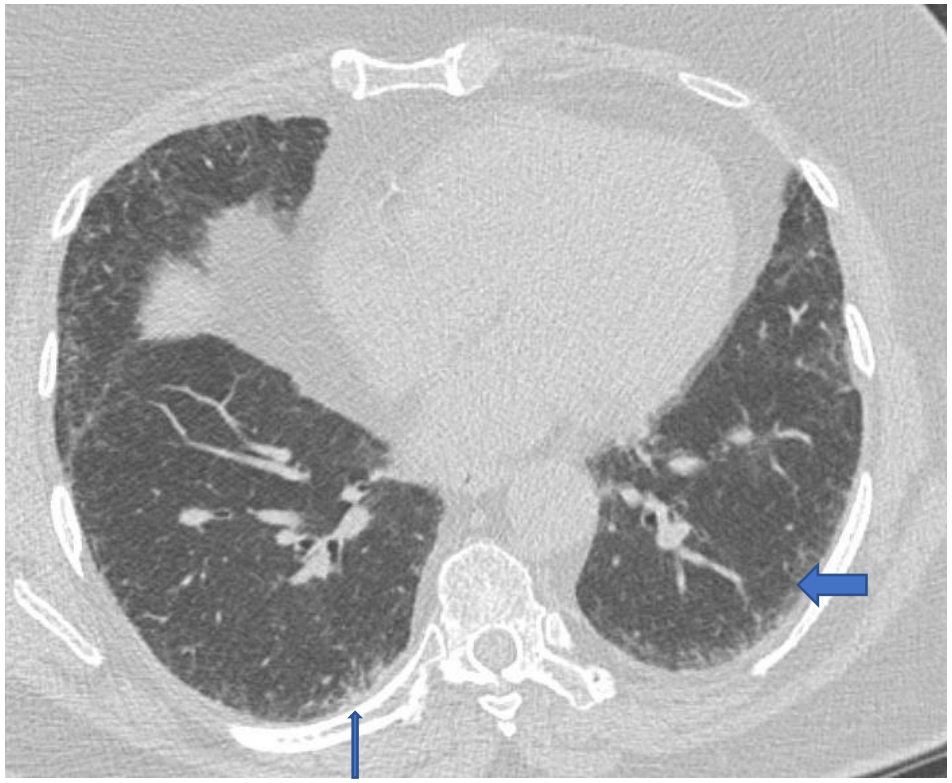


Teaching points

- This person has ILA
- What is this? Will this progress?
- Should the person get a lung biopsy? Is this early UIP?
- Is there data to support the use of anti-fibrotics now ? (No, but a trial in early disease might help)
- If not, how would you follow this patient?

RA lung therapies: what type and for whom?

- For inflammatory disease like COP and cellular NSIP: corticosteroids alone or in combination with additional treatments (Rituxan , MMF, AZA, maybe Abatacept)
- Special circumstances: Rheumatoid nodulosis, bronchiolitis (Rituxan)
- Obliterative Bronchiolitis: there is no documented Rx except lung transplant but many try Rituxan.
- ILD: FDA approved and newer emerging anti-fibrotics need to be considered.
- We are not certain the role of MMF in RA ILD but many use it.

So if treatment options exist in RA ILD , should we screen and if so how?

Screening strategies in RA/ILD in 2022 absent great biomarkers

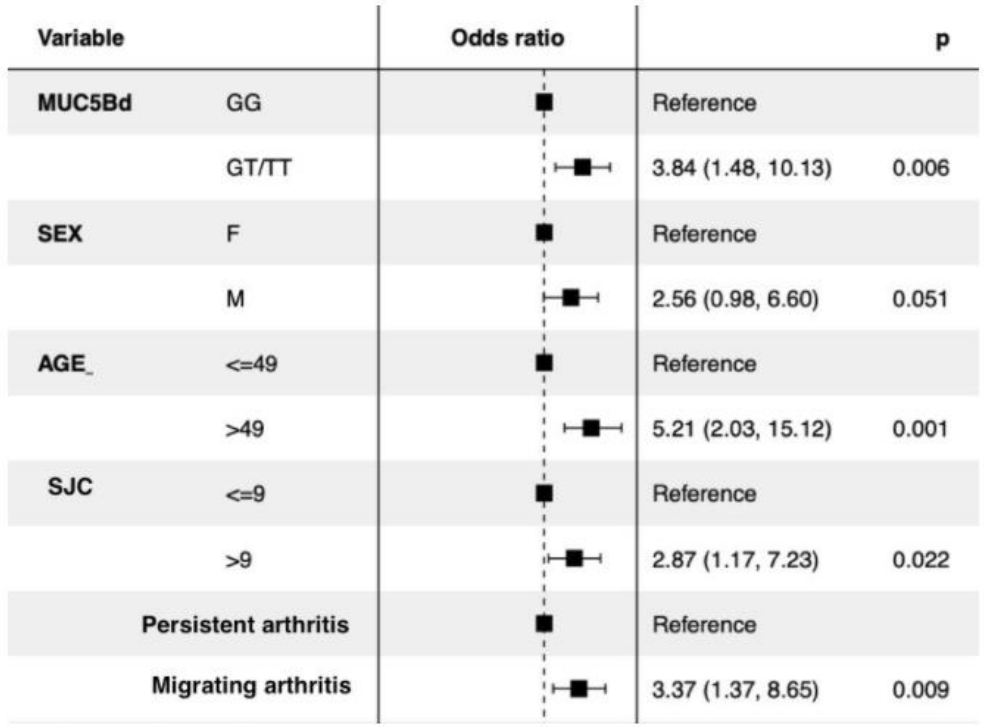
MUC5B Promoter Variant rs35705950 and Risk Stratification for Rheumatoid Arthritis – Interstitial Lung Disease

Pierre-Antoine Juge[1] et al

(ACR Nov 2020)

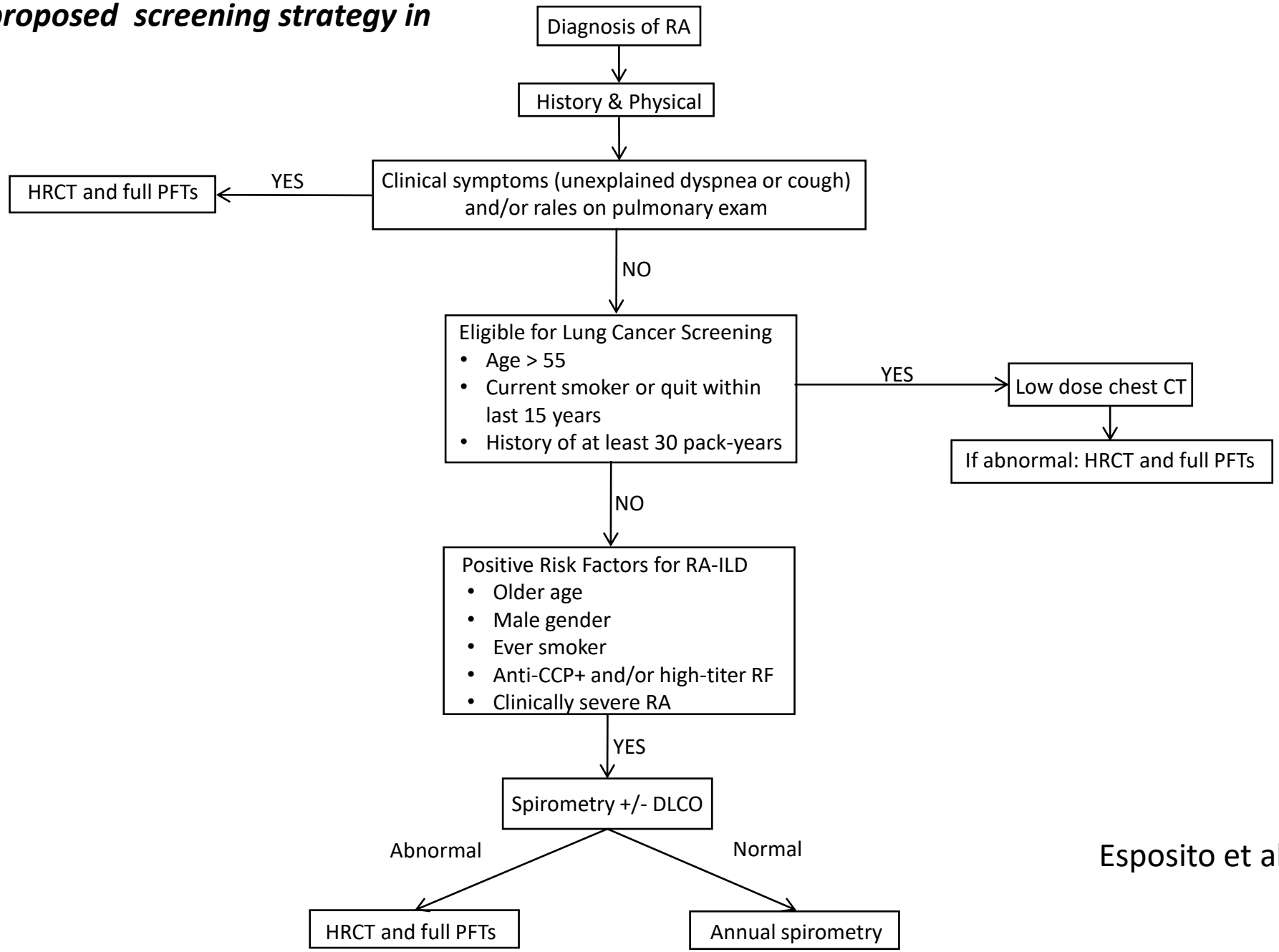
Conclusion: In RA patients, altogether with baseline clinical data, *MUC5B*rs35705950 genotyping could help to improve risk stratification for ILD occurrence at 13 years of RA duration.

Variable		Odds ratio	p
MUC5Bd	GG	Reference	
	GT/TT	3.84 (1.48, 10.13)	0.006
SEX	F	Reference	
	M	2.56 (0.98, 6.60)	0.051
AGE_	<=49	Reference	
	>49	5.21 (2.03, 15.12)	0.001
SJC	<=9	Reference	
	>9	2.87 (1.17, 7.23)	0.022
Persistent arthritis		Reference	
Migrating arthritis		3.37 (1.37, 8.65)	0.009



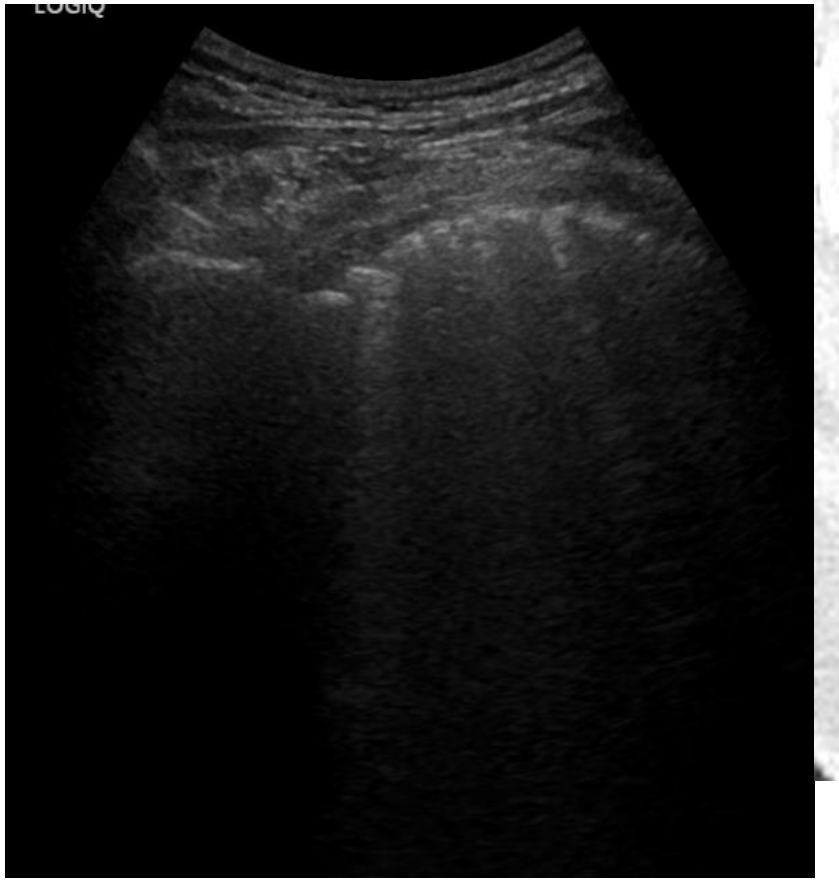
Baseline predictors of ILD occurence at 13 years of RA duration

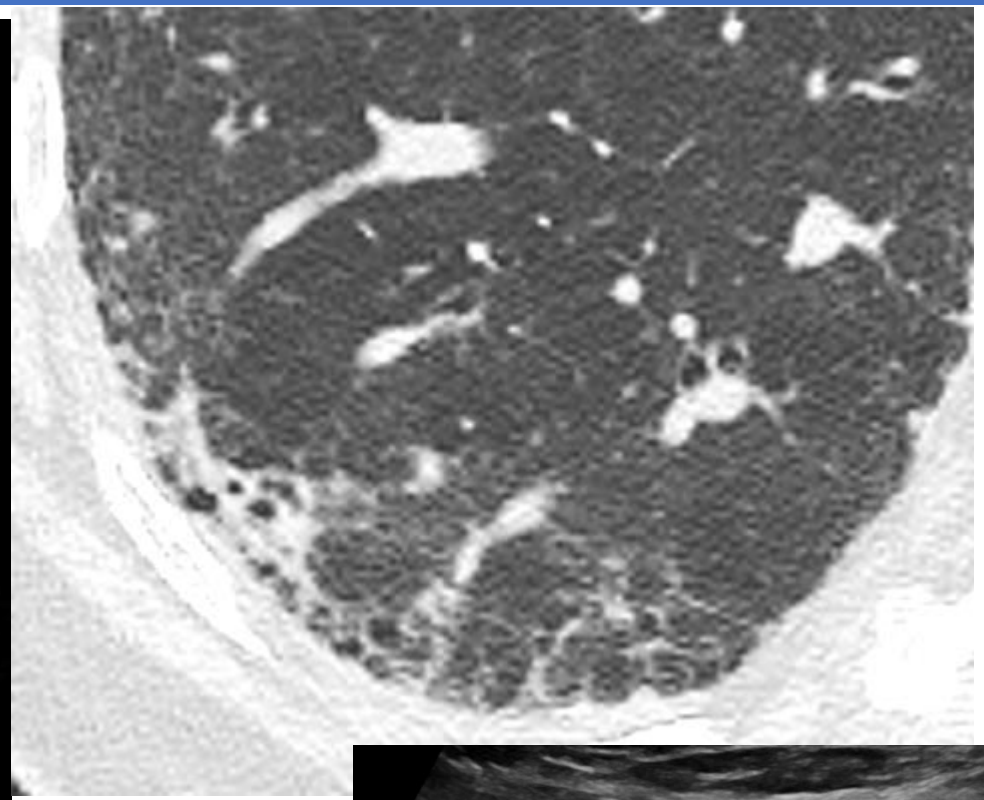
Option 1: proposed screening strategy in RA ILD

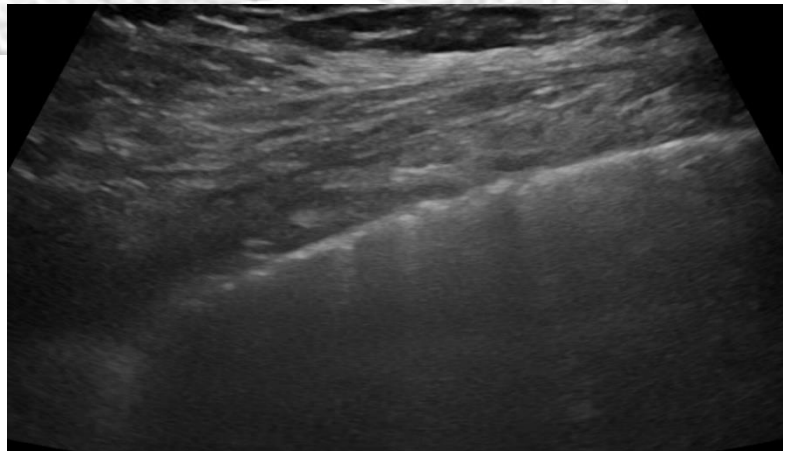


Esposito et al 2019

76 yr. female, RA diag in 2014,MTX /HCQ . DAS score high for 18 months. CXR abnormal prior to biologic screening. CT scan 2017 & 2019







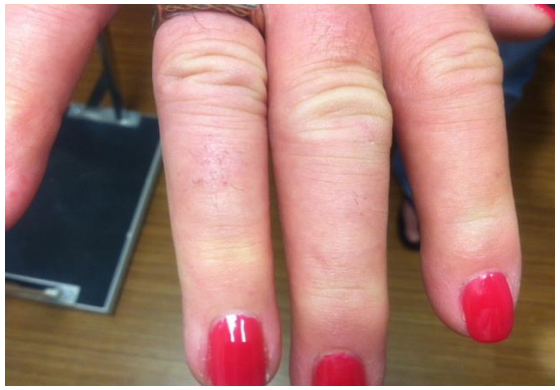
Courtesy of Koduri G

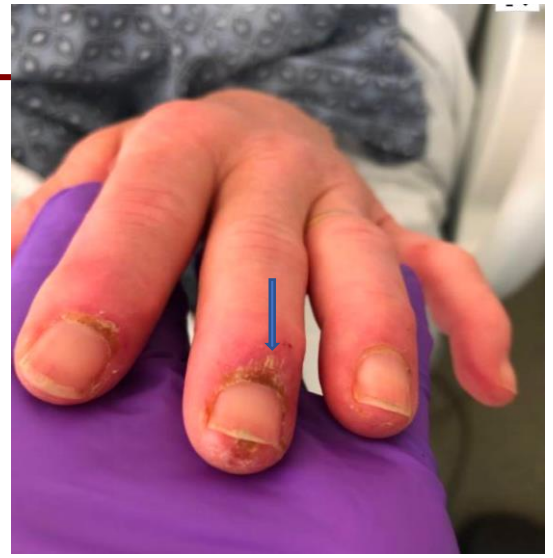
Systemic Sclerosis (SSc)

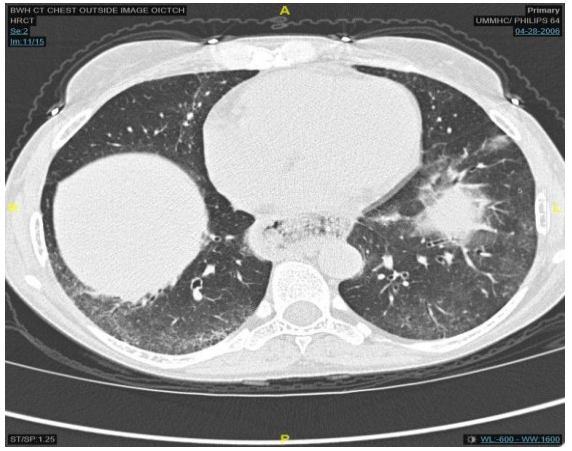
- Chronic fibrosing disorder characterized by autoimmunity vasculopathy and fibrosis

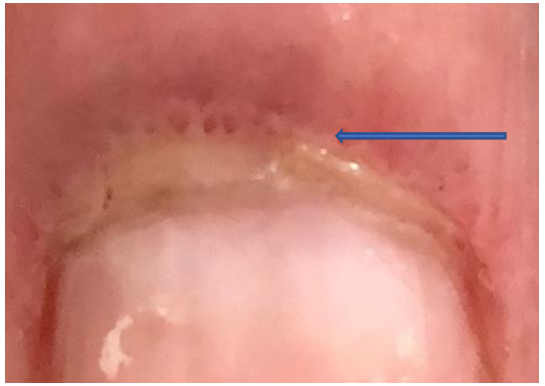
- Key clinical features:

  - Interstitial Lung Disease
  - Pulmonary Hypertension
  - Esophogeal and GI dysmotility:ASPIRATION
  - Renal crisis
  - Pericardial and myocardial disease









ILD and Scleroderma: higher risk populations and phenotypes.

- Scl-70 ab + (newer antibodies include Th/To and U11-12)
- Diffuse skin disease, digital ulcers, arthritis, indicate higher risk
- Age (older)
- FVC and DLCO decline over 2 years (Volkmann E et al Ann Rheum Dis 2018)
- African American or Native American
- Extent of disease on CT(> 20% of HRCT involved) (TA Winstone et al Chest 2014)
- >20% fibrosis on CT and FVC<70%) (AJRCCM 2008)
- Composite PFTs and clinical decline (Goh et al 2018)

Loss of Lung function occurs early in SSc The First 5 years are key. (Steen et al Arthritis Rheum 1994)

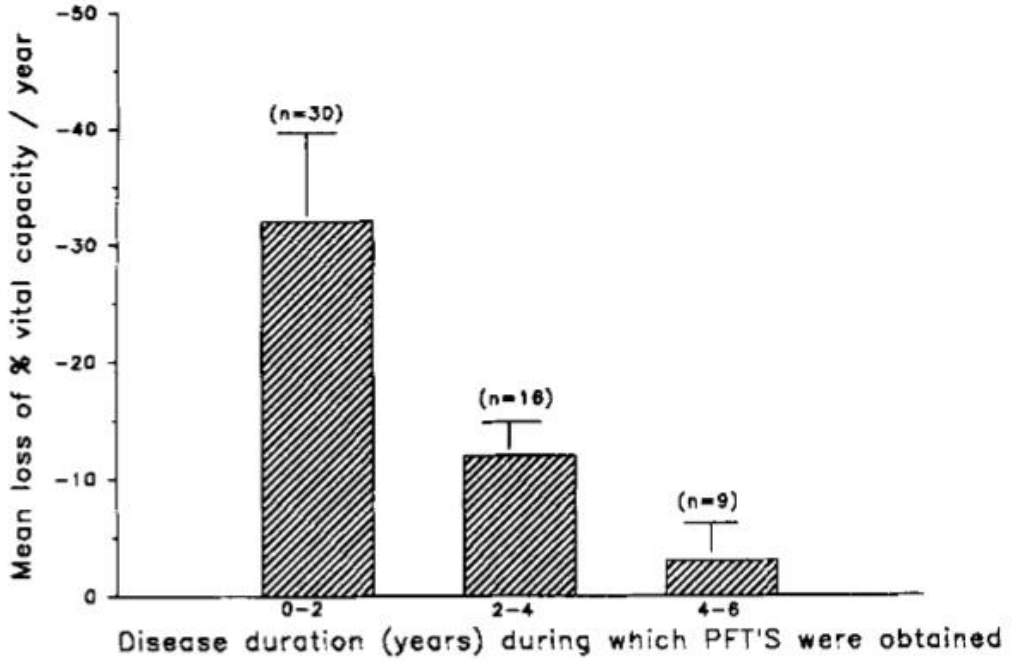
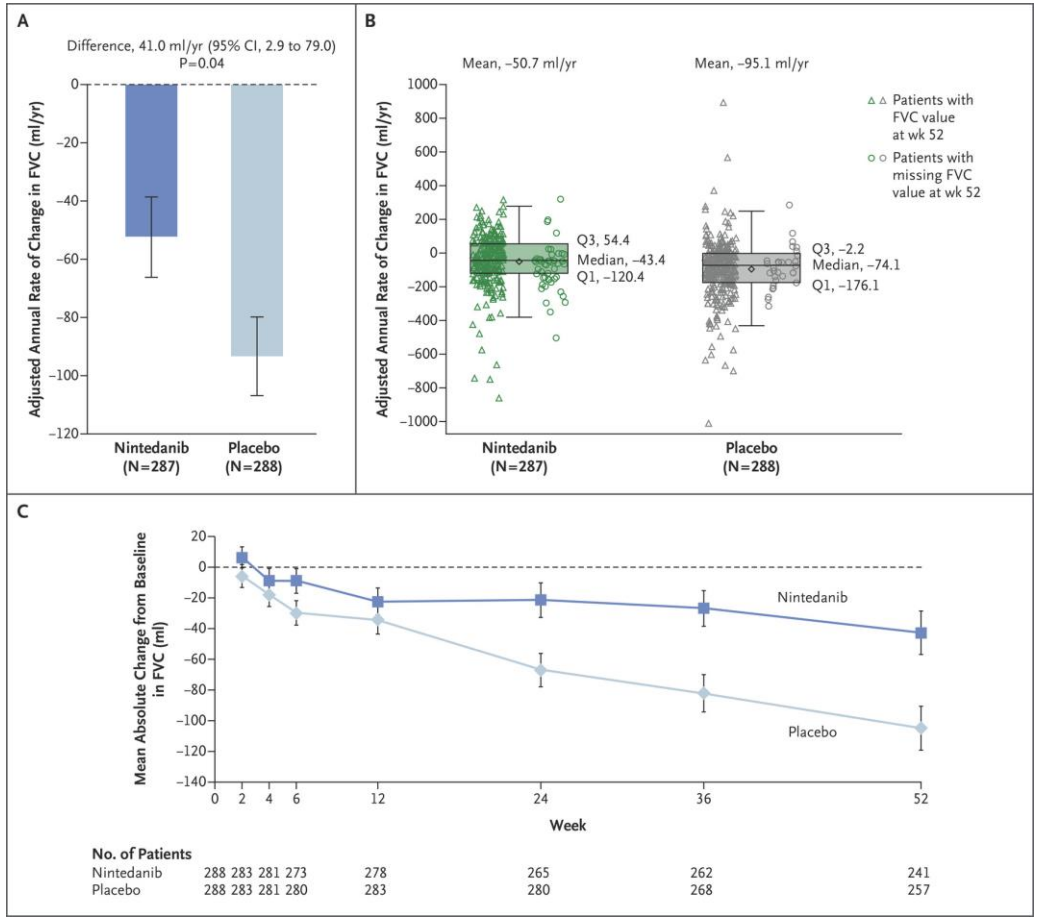
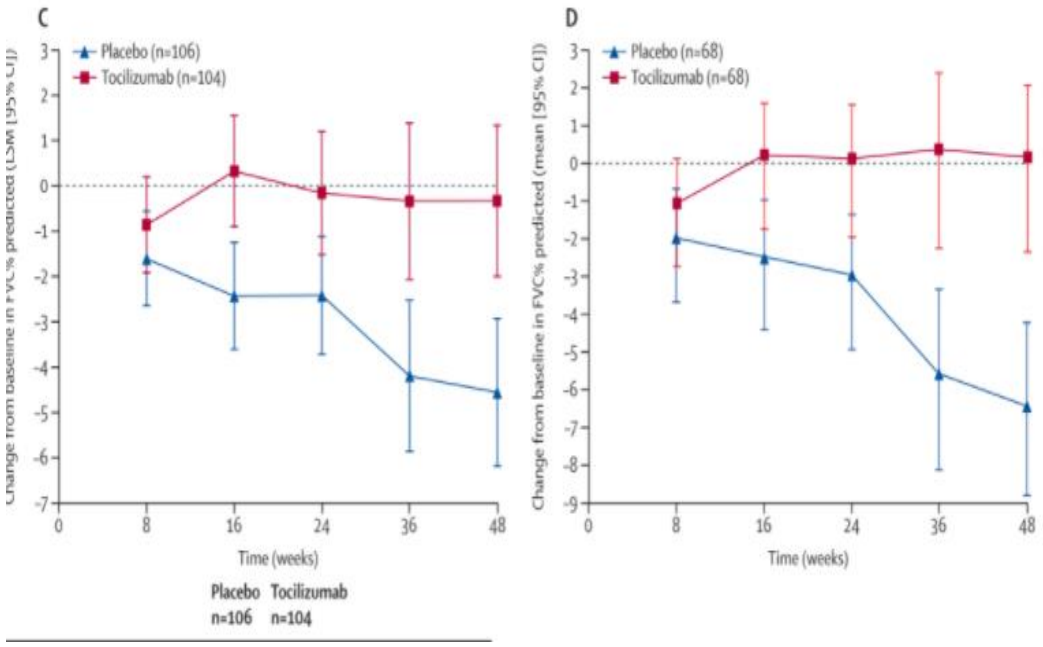


Figure 1. Mean loss of percent vital capacity occurring over 2-year time periods in 55 patients whose initial pulmonary function tests (PFT's) were performed during the first 5 years of scleroderma symptoms.

Distler O et al : SENSCIS Trial NEJM June 2019



Tocilizumab and Phase III trial (focuSSced Khanna et al Lancet Resp 2020)



- No difference in MRSS (primary end point)
- There was a difference in decline in FVC compared to placebo
- Difference in decline in FVC (LSM) was 4.2% favoring TCZ over placebo in all patients and 6.5 % in those with ILD.
- >10% decline in FVC % occurred in 17% of placebo and 5% of TCZ

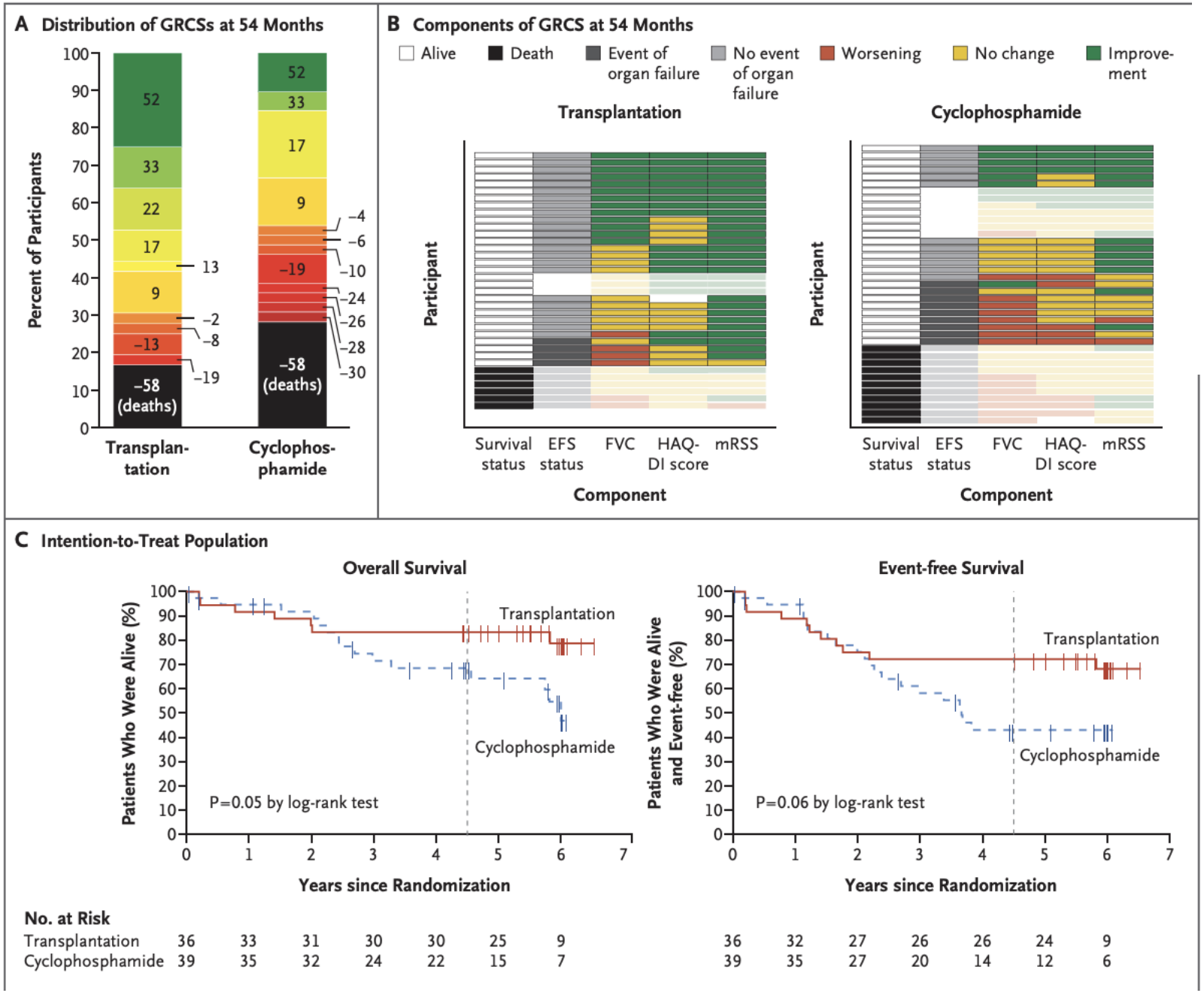
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma

K.M. Sullivan, E.A. Goldmuntz, L. Keyes-Elstein, P.A. McSweeney, A. Pinckney, B. Welch, M.D. Mayes, R.A. Nash, L.J. Crofford, B. Eggleston, S. Castina, L.M. Griffith, J.S. Goldstein, D. Wallace, O. Craciunescu, D. Khanna, R.J. Folz, J. Goldin, E.W. St. Clair, J.R. Seibold, K. Phillips, S. Mineishi, R.W. Simms, K. Ballen, M.H. Wener, G.E. Georges, S. Heimfeld, C. Hosing, S. Forman, S. Kafaja, R.M. Silver, L. Griffing, J. Storek, S. LeClercq, R. Brasington, M.E. Csuka, C. Bredeson, C. Keever-Taylor, R.T. Domsic, M.B. Kahaleh, T. Medsger, and D.E. Furst, for the SCOT Study Investigators*

6% treatment related mortality in SCT group at 72mo



Contemporary Treatment in SSc: MMF still the cornerstone of therapy

- SLS I,II (Cyclophosphamide, **but now most of use MMF**)
- Nintedanib in SSc (SENCIS trial)
- Myeloablative therapy (NEJM 2018) :rapidly progressive ILD
- IL-6 receptor antibody (Lancet Resp Med 2020)
- SLS III: randomized trial using Pirfenidone vs SOC (stopped)
- INBUILD trial (PF- ILD non IPF) (+ trial but small number of scleroderma pts)
- Rituximab (small studies)
- Inhaled Treprostinil in ILD? (Nathan S et el Lancet Resp 2021)

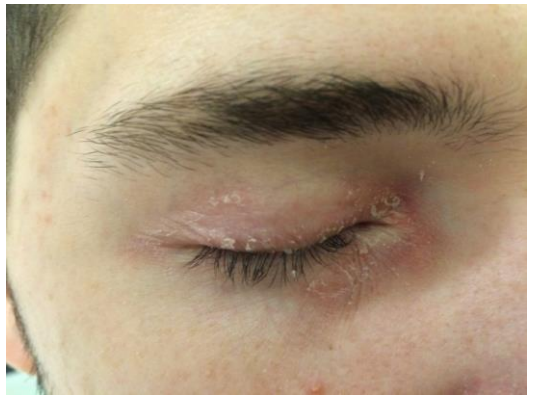
How do these trials change practice ?

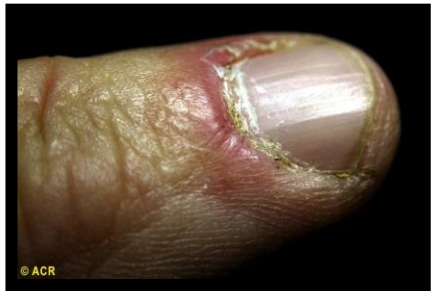
- FDA approval for antifibrotics and IL-6 therapy in SSc ILD can affect the way we practice and identify and refer for ILD assessment and treatment.
- The results of the antifibrotics are modest: these drugs are not blockbusters.
- If a patient is stable on MMF and has fibrosis is there any reason to add on anti-fibrotic if lung function stable?
- If they are not stable on MMF then adding or changing to antifibrotic may be reasonable.
- When to use IL-6 (Tocilizumab) ? Early ? Evidence of inflammatory markers
- Therapies for ILD and fibrosis are evolving with many ongoing trials.

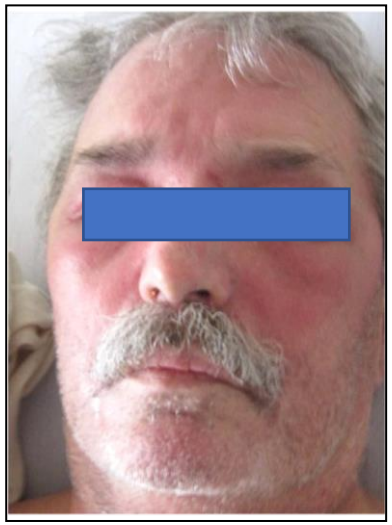
Inflammatory Myositis and the lung

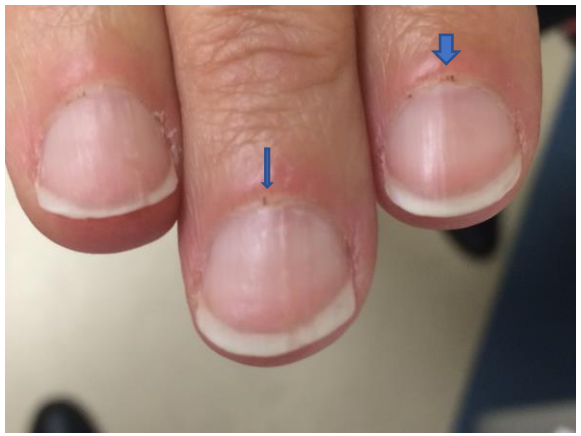
- *Interstitial lung disease* (NSIP, rarely UIP), *Organizing pneumonia (OP)*
- *Antisynthetase syndrome* (fever, Raynauds, arthritis, myositis, mechanics hands,ILD) (often NSIP or OP or both)
- MDA5 (can be associated with AIP)
- Respiratory muscle dysfunction
- Diaphragmatic dysfunction

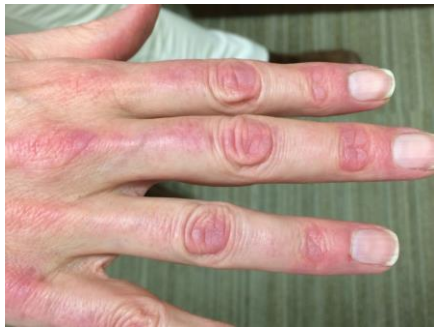
Teaching Phenotypes:**Look at the hands! Look at the skin**!



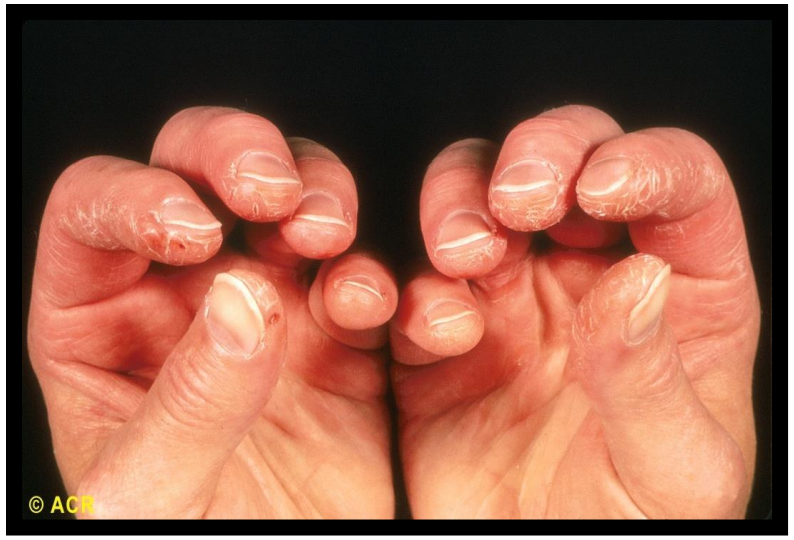


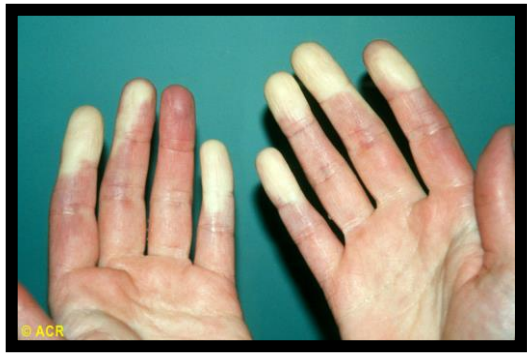


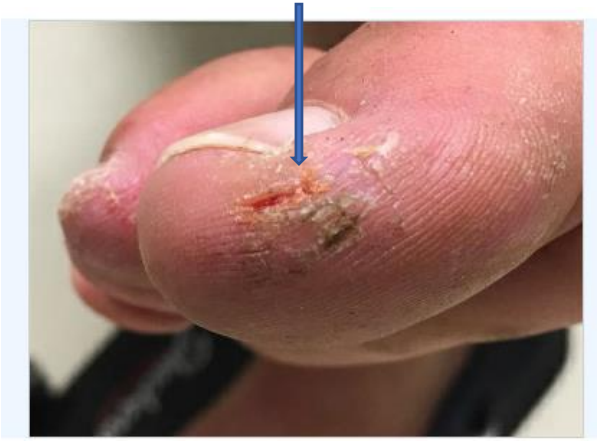




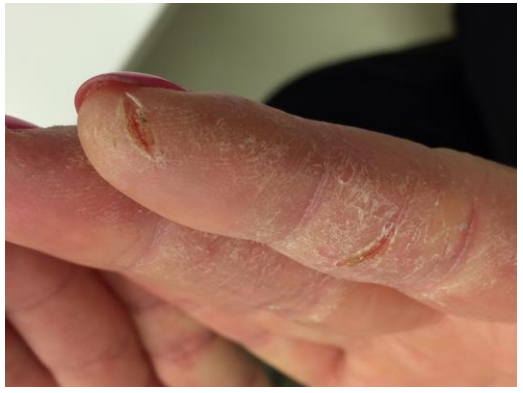
Antisynthetase Syndrome

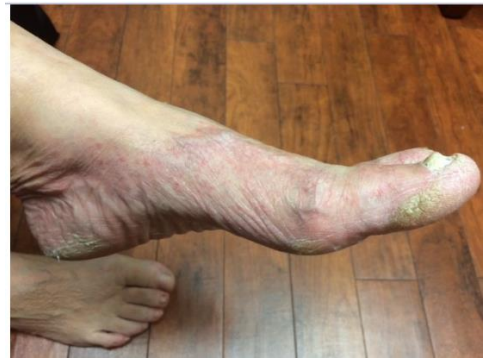






Fever
Raynaud's
Inflammatory Arthritis
Mechanics hands
ILD





Solomon et al (2011) [10]

Required: Presence of anti-aminoacyl tRNA synthetase antibody

PLUS *two major* or *one major and two minor criteria*:

Major:

1. Interstitial Lung Disease (not attributable to another cause)
2. Polymyositis or dermatomyositis by Bohan and Peter critieria

Minor:

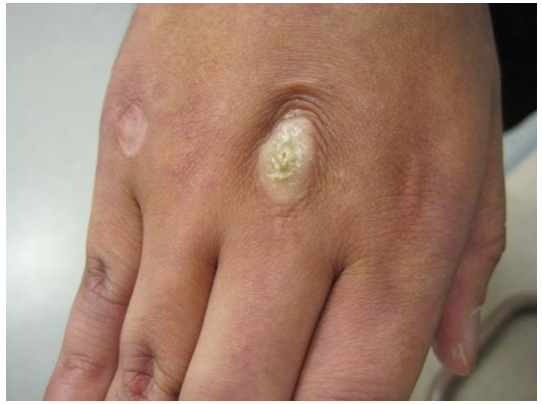
1. Arthritis
2. Raynaud's phenomenon
3. Mechanic's hands

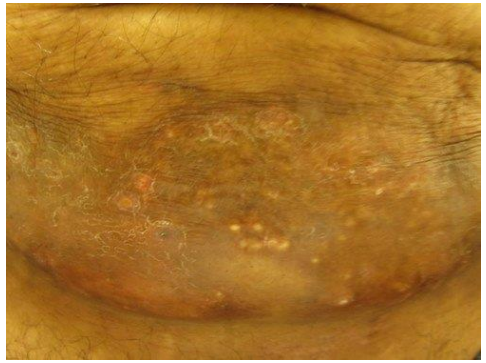
Witt LJ et al. Clin Pulm Med. 2016 Sep; 23(5): 218–226.

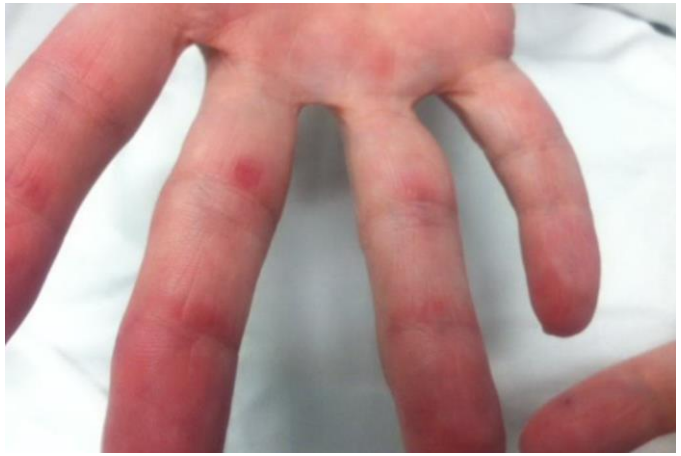
Antibodies in myositis and ILD:summary

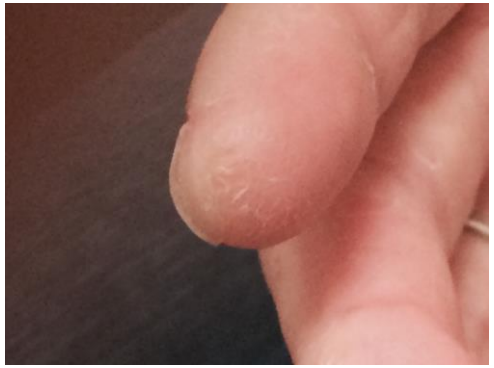
- Antisynthetase abs: Jo-1,PL-7, PL-12, EJ, OJ, KS, ZO , HA.
- Overlap antibodies: RNP, PML/Sc.
- Antibodies associated with malignancy in DM (p155/140):
- (protective for ILD)
- **Amyopathic antibodies**: **anti-MDA5, can result in rapidly progressive ILD**
- **SUMO ab: small ubiquitin-like modifier activating enzyme seen in DM/ILD**

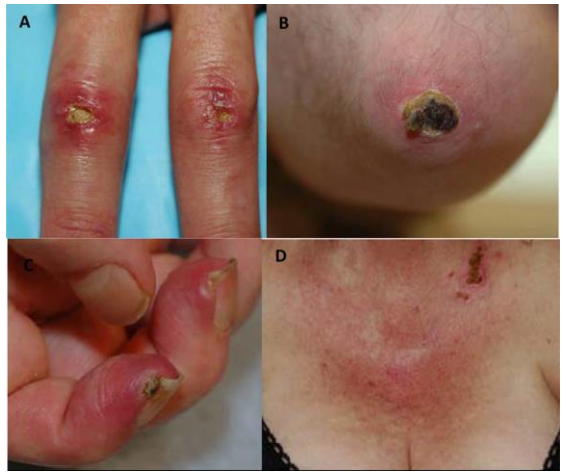
Phenotype skin MDA 5: high risk of rapidly progressive ILD inc AIP pattern





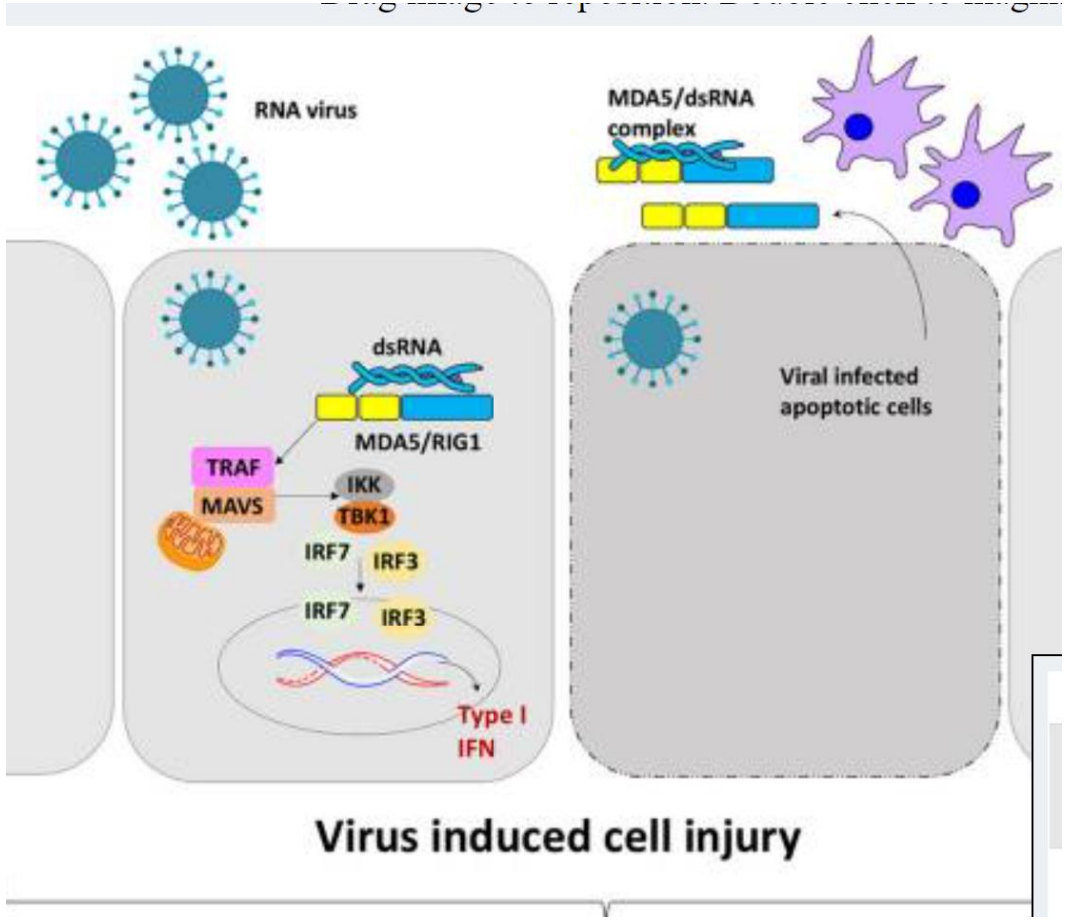




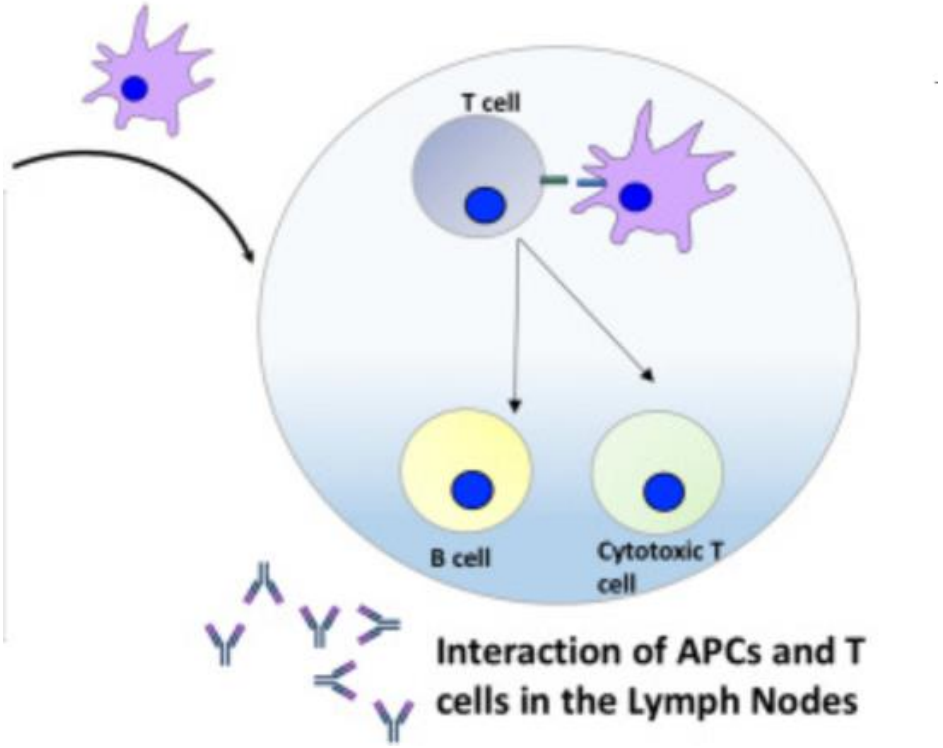


Narang et al
Arthritis Care
2015;67(5)

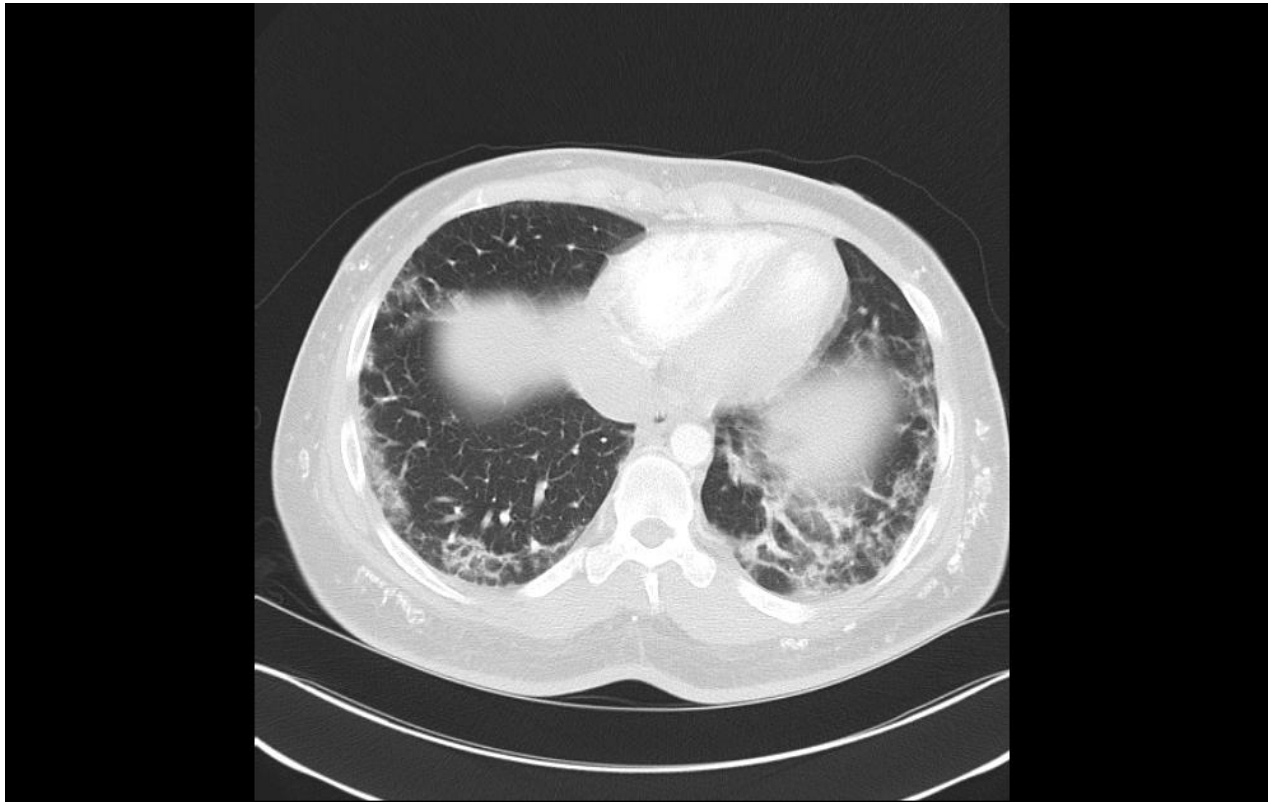
MDA5

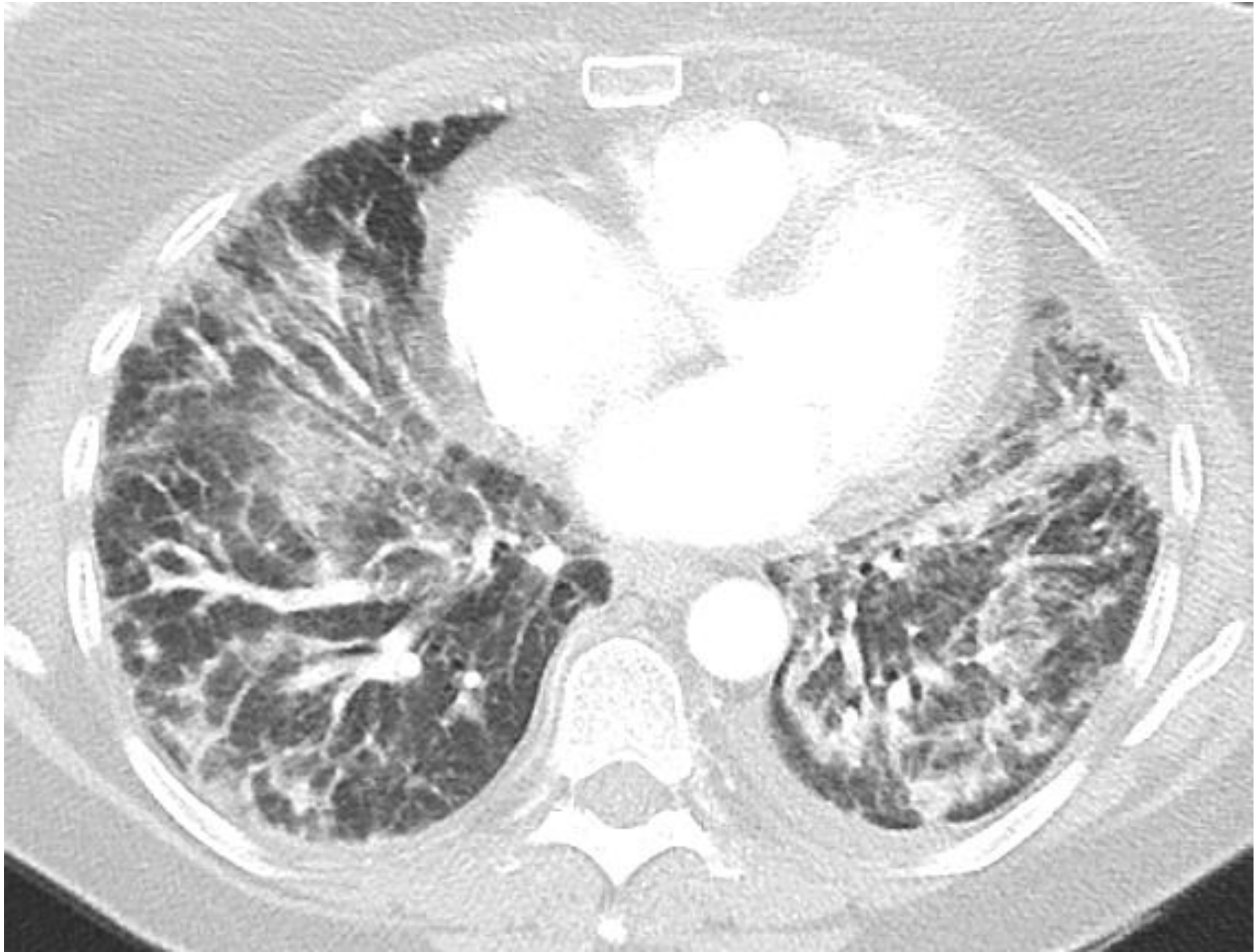


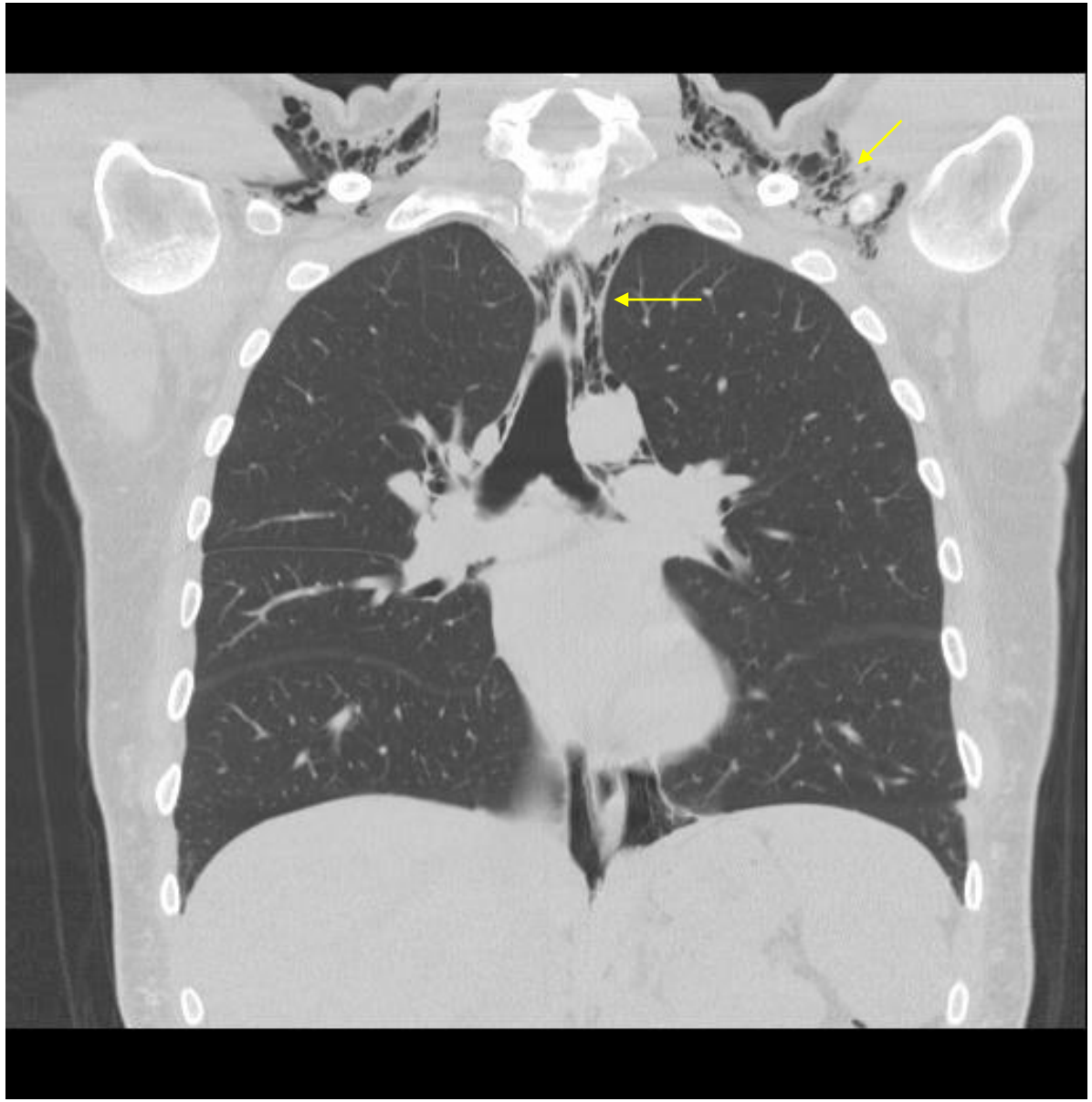
Mehta P et al Rheum Int 2021



Lung Phenotype: ILD can include OP, AIP (diffuse alveolar damage) and pneumomediastinum







MDA 5 and COVID 19: what is the relationship?

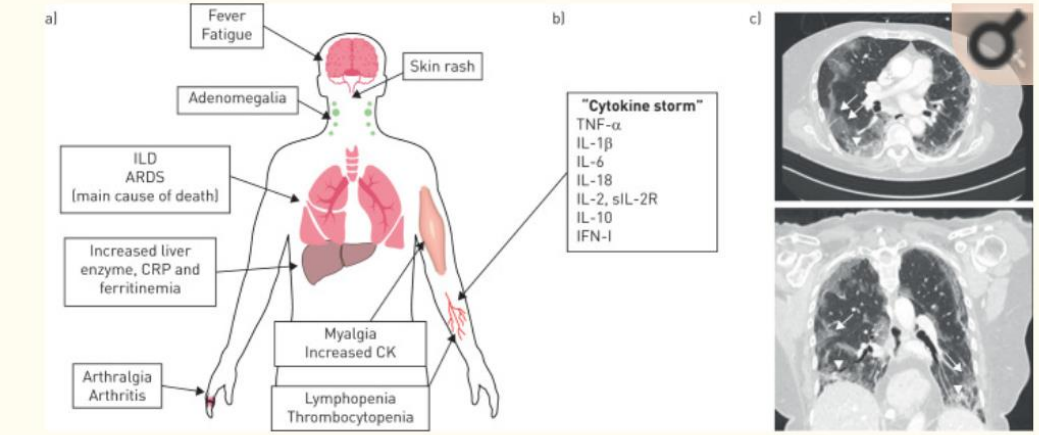


FIGURE 1

a) Clinical and biological features of anti-MDA5 syndrome. b) Cytokines whose levels are increased in anti-MDA5 syndrome patients' serum. c) High-resolution computed tomography of an anti-MDA5 syndrome patient, showing bilateral peripheral subpleural ground-glass opacities prevailing in the lower lobes (arrows), with limited consolidation (arrowheads). ILD: interstitial

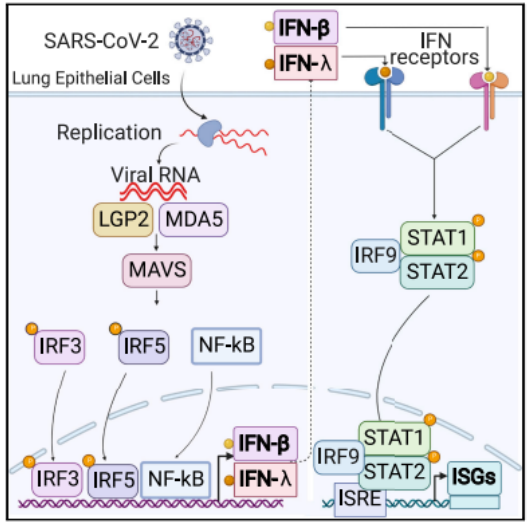
Giannini et al Eur

Article

Cell Reports

MDA5 Governs the Innate Immune Response to SARS-CoV-2 in Lung Epithelial Cells

Graphical Abstract



Authors

Xin Yin, Laura Riva, Yuan Pu, ..., Judd F. Hultquist, Adolfo García-Sastre, Sumit K. Chanda

Correspondence

schanda@sbpdiscovery.org

In Brief

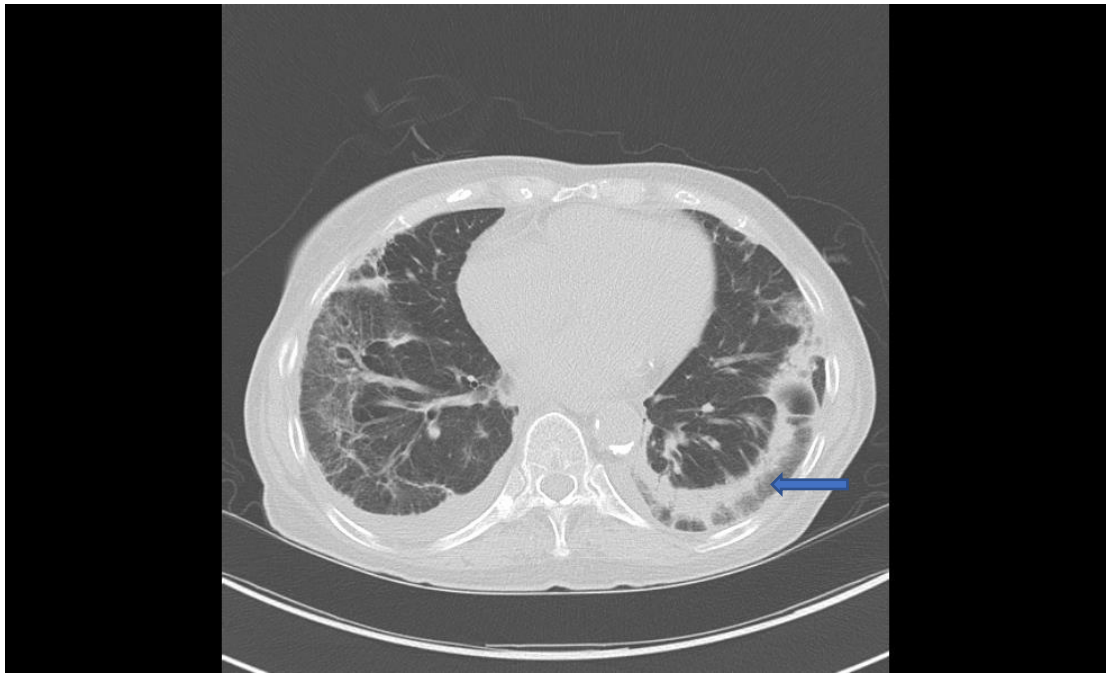
The molecular events that underlie innate immune recognition and response to SARS-CoV-2 infection remain unclear. Yin et al. report that SARS-CoV-2 replication induces a delayed interferon (IFN) response that is triggered by sensing of viral RNA through the MDA5 pattern recognition receptor.

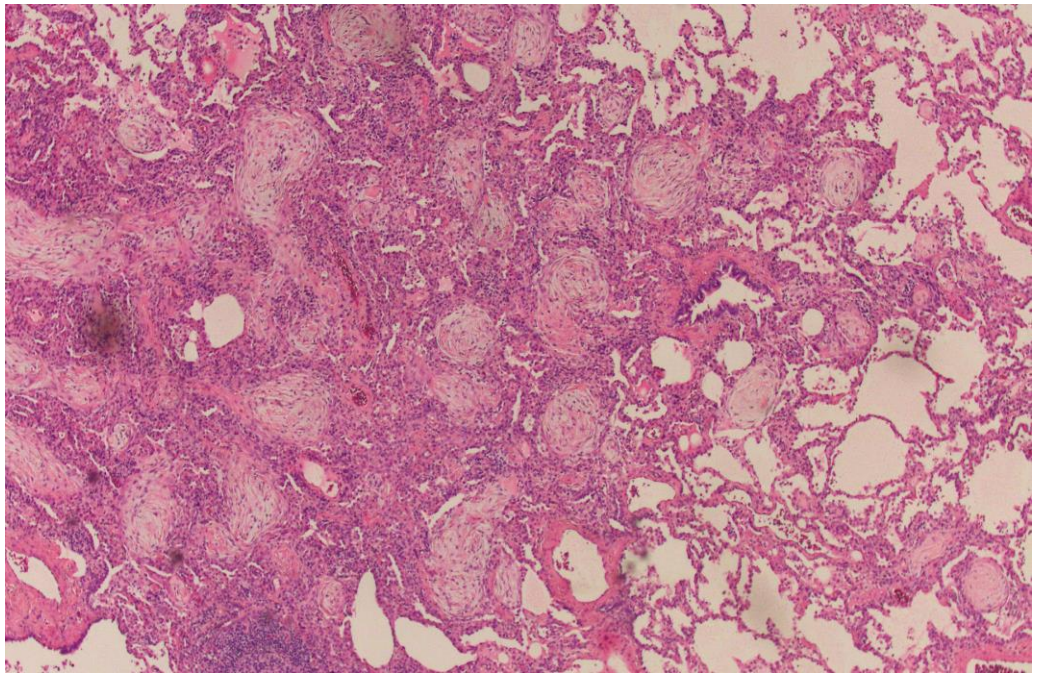
Highlights

- SARS-CoV-2 replication induces a delayed IFN response in lung epithelial cells
- MDA5 and LGP2 are the major sensors recognizing SARS-CoV-2 infection
- Viral intermediates activate the IFN response through MDA5-mediated sensing
- IRF3, IRF5, and NF-κB/p65 are required for the IFN response induced by SARS-CoV-2

Yin et al., 2021, Cell Reports 34, 108628
January 12, 2021 © 2020 The Authors.

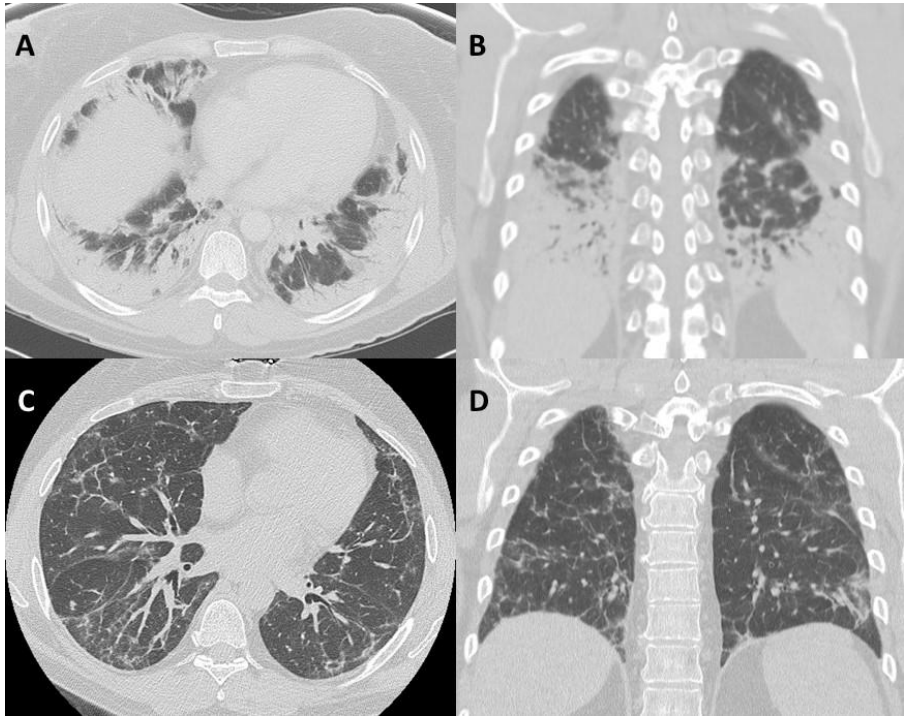
Case: Typical CT finding in antisynthetase ILD:39 yo female with weakness, dyspnea and elevated CK : Jo-1+. What pathology does this CT suggest? Note the Atoll sign on CT, which correlates with organizing pneumonia



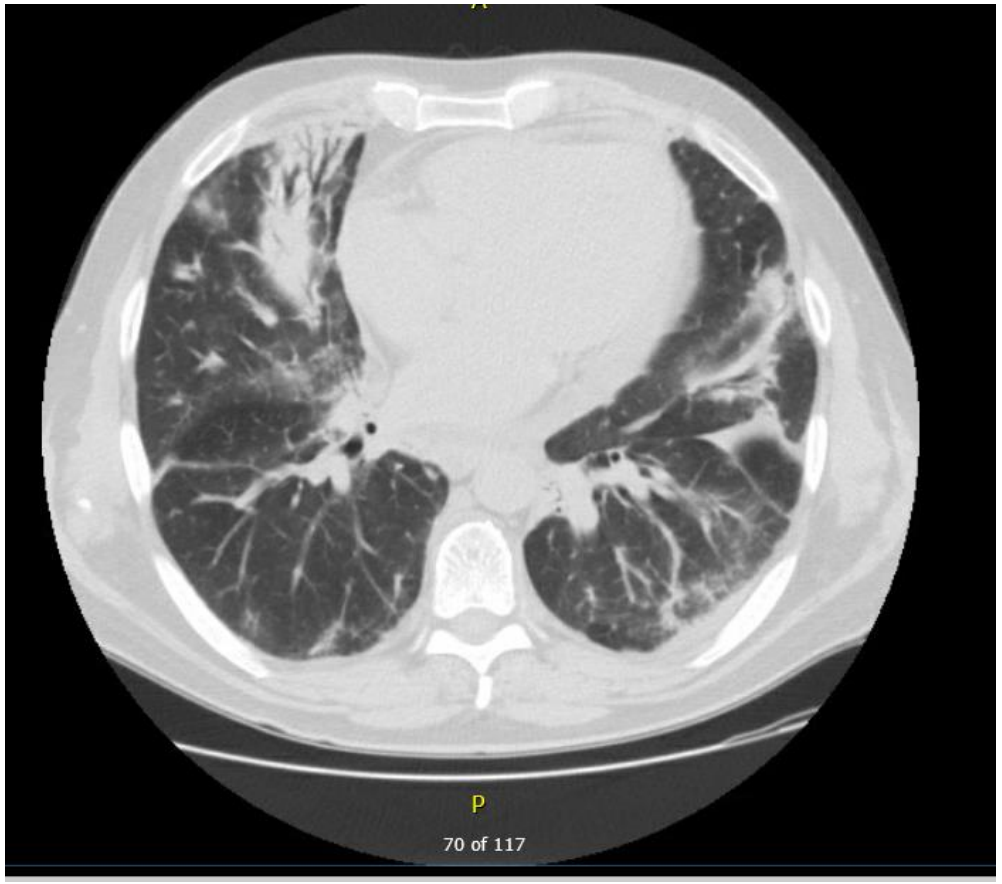


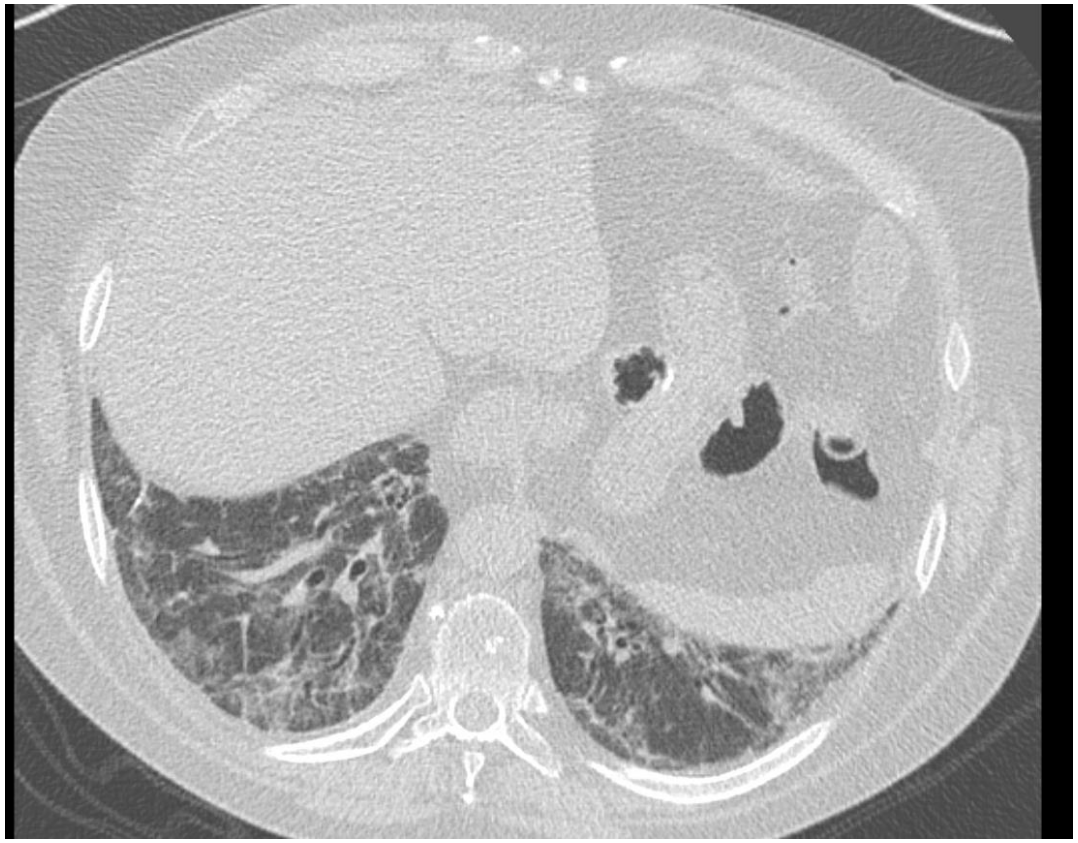
Path showed Organizing pneumonia(OP) and NSIP:Initially treated with CS and MMF, prednisone, incomplete response (muscle and lung) so Rituxan added with success. **FVC 100% DLCO 72%.**

Anti-inflammatory therapy can work for this group of patients



Caution!: Inflammatory disease can evolve to fibrotic phenotype (Jo-1+ 2014 and then 2019)





Treatment in ILD/IIM

Corticosteroids nearly always in combination with another agent typically MMF or AZA

Tacrolimus in cases that don't respond or in MDA 5

Rituxan or Cyclophosphamide (often for severe disease)

JAK inhibitors (limited data MDA5)

IVIG often in cases that fail to respond to CS/MMF or AZA (Huapaya et al Resp Med 2019)

Will some of these pts need antifibrotic therapy?

Ongoing Trial: ATTACK MY ILD: Abatacept in antisynthetase ILD *

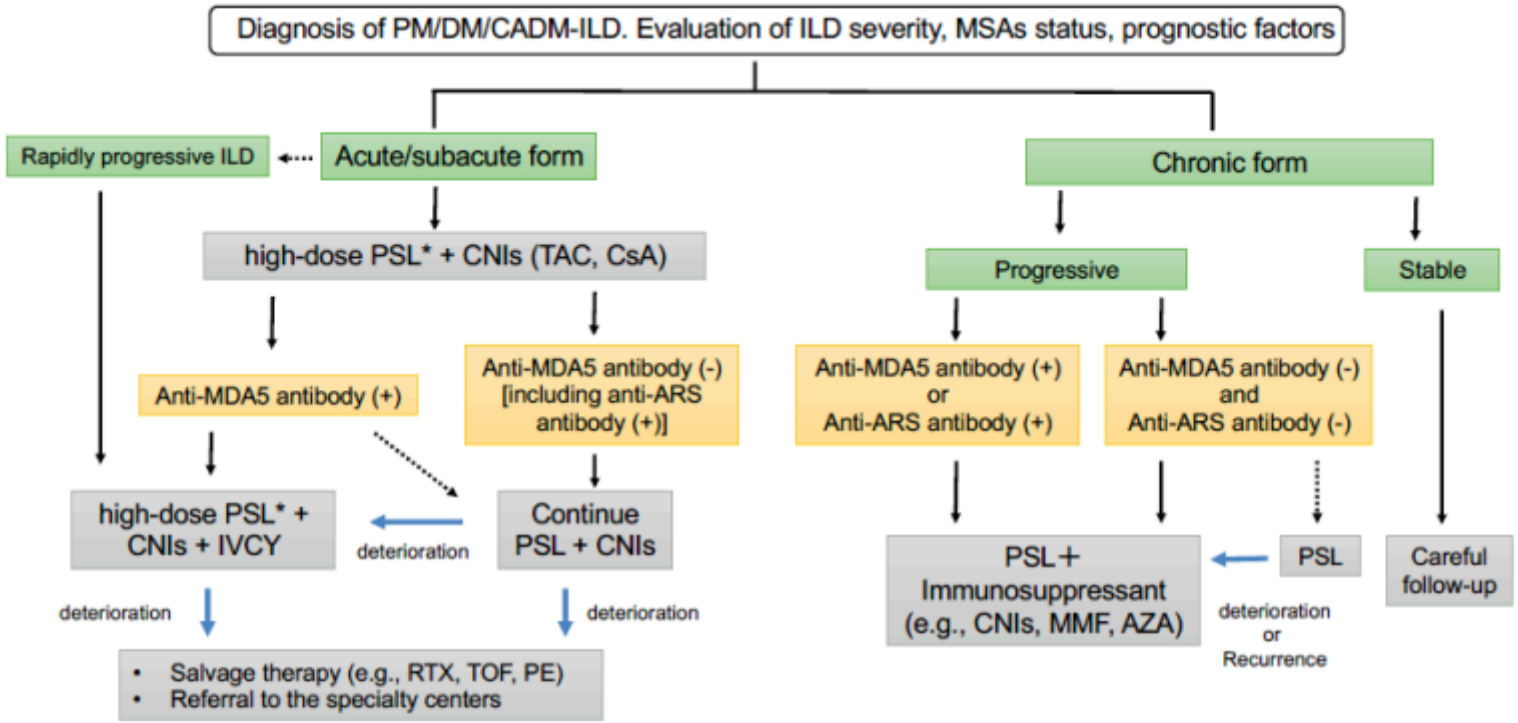
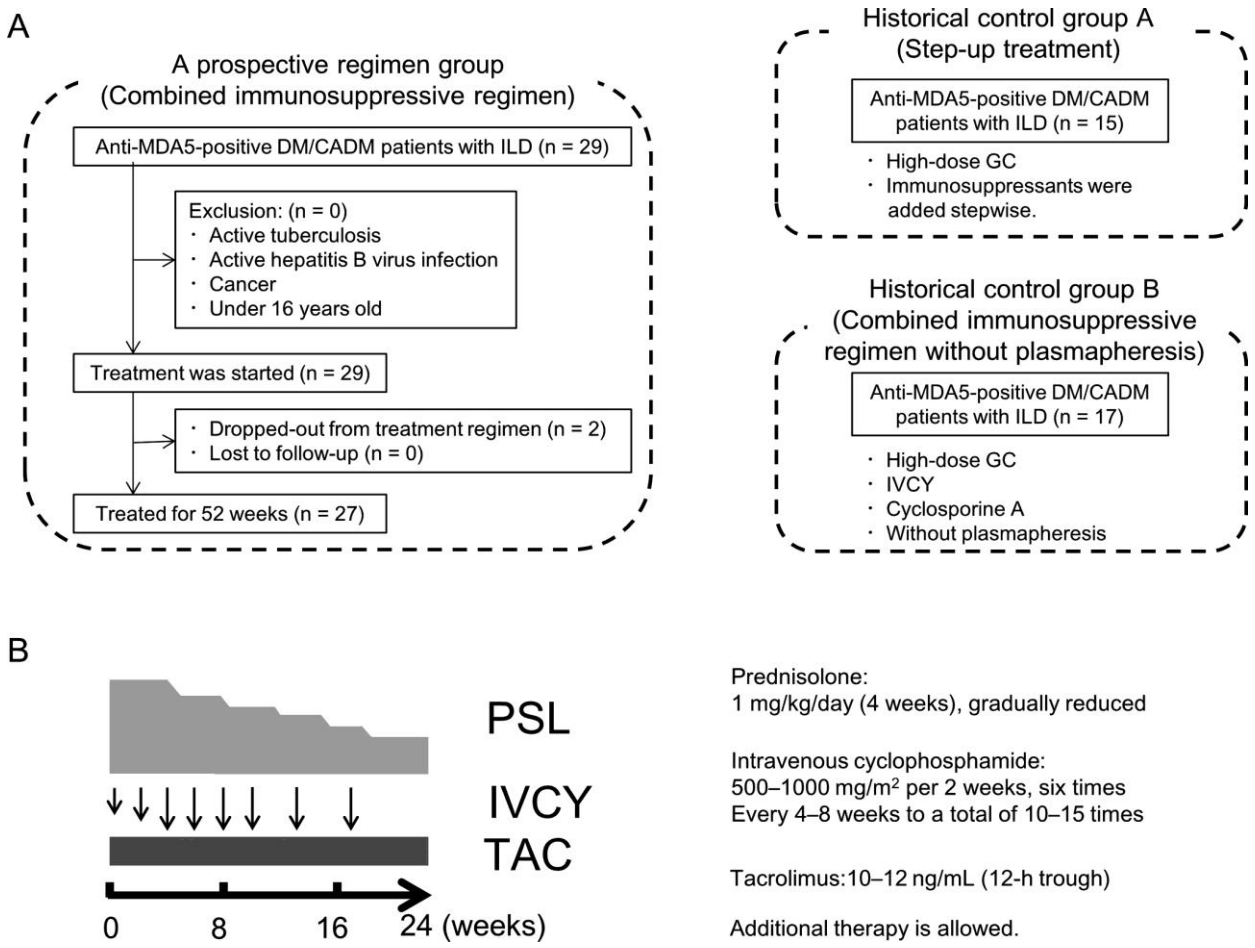


Figure 1. Proposal of a treatment algorithm for patients with PM-/DM-/CADM-ILD. * Methylprednisolone pulse therapy (1000 mg/day intravenous for 3 days) should be considered for severe ILD. PM—polymyositis; DM—dermatomyositis; CADM—clinically amyopathic DM; ILD—interstitial lung diseases; MSAs—myositis-specific autoantibodies; PSL—prednisolone; CNIs—calcineurin inhibitors; TAC—tacrolimus; CsA—cyclosporin A; MDA5—melanoma differentiation-associated gene 5; ARS—aminoacyl tRNA synthetase; IVCY—intravenous cyclophosphamide; MMF—mycophenolate mofetil; AZA—azathioprine; RTX—rituximab; TOF—tofacitinib; PE—plasma exchange.

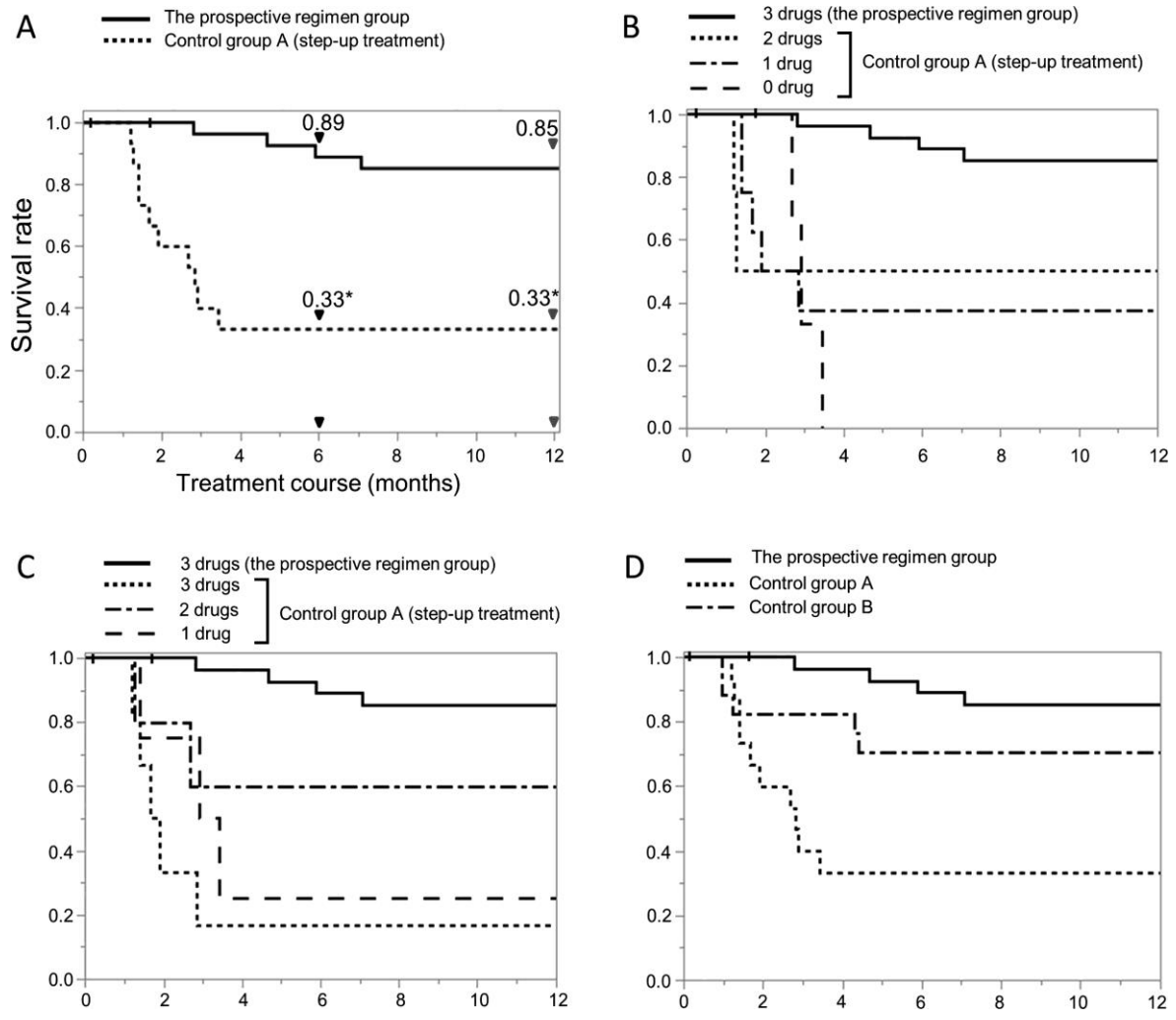
Fujisawa T Medicina 2021

Multicenter Prospective Study of the Efficacy and Safety of Combined Immunosuppressive Therapy With High-Dose Glucocorticoid, Tacrolimus, and Cyclophosphamide in Interstitial Lung Diseases Accompanied by Anti–Melanoma Differentiation–Associated Gene 5–Positive Dermatomyositis



Arthritis & Rheumatology, Volume: 72, Issue: 3, Pages: 488-498, First published: 16 September 2019, DOI: (10.1002/art.41105)

Multicenter Prospective Study of the Efficacy and Safety of Combined Immunosuppressive Therapy With High-Dose Glucocorticoid, Tacrolimus, and Cyclophosphamide in Interstitial Lung Diseases Accompanied by Anti–Melanoma Differentiation–Associated Gene 5–Positive Dermatomyositis



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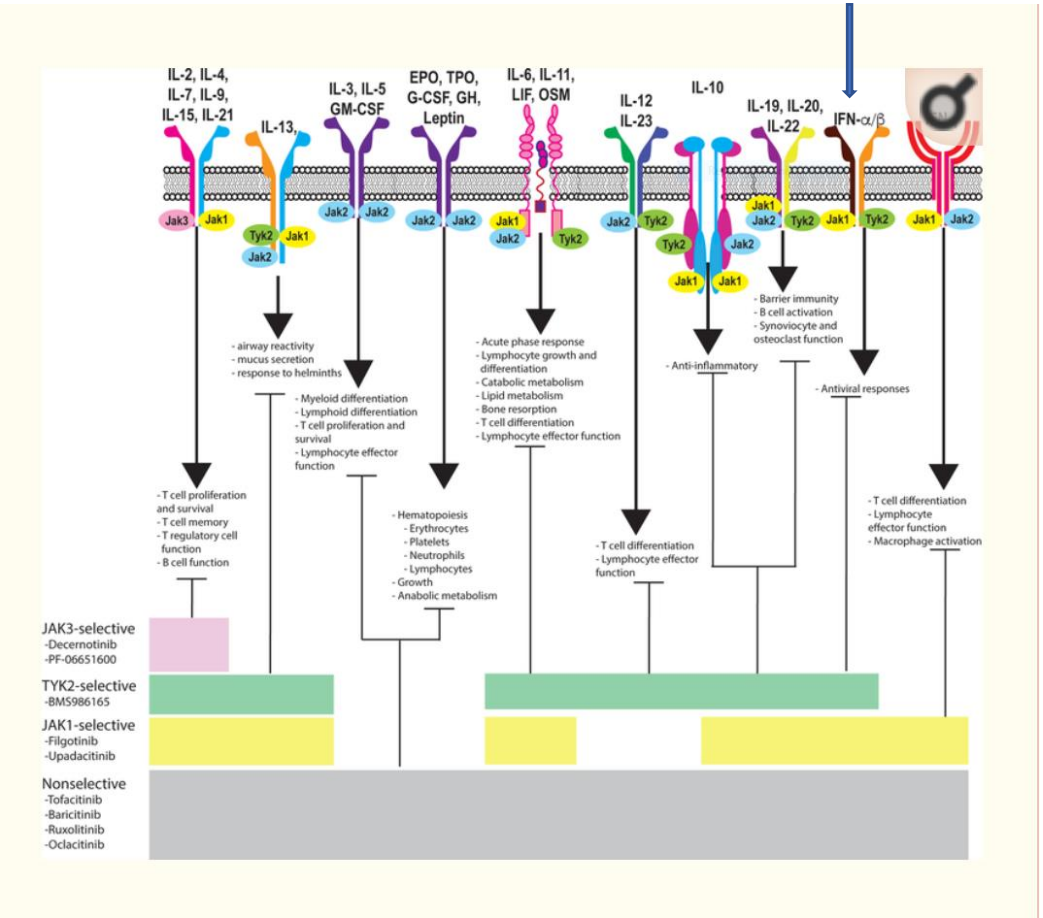
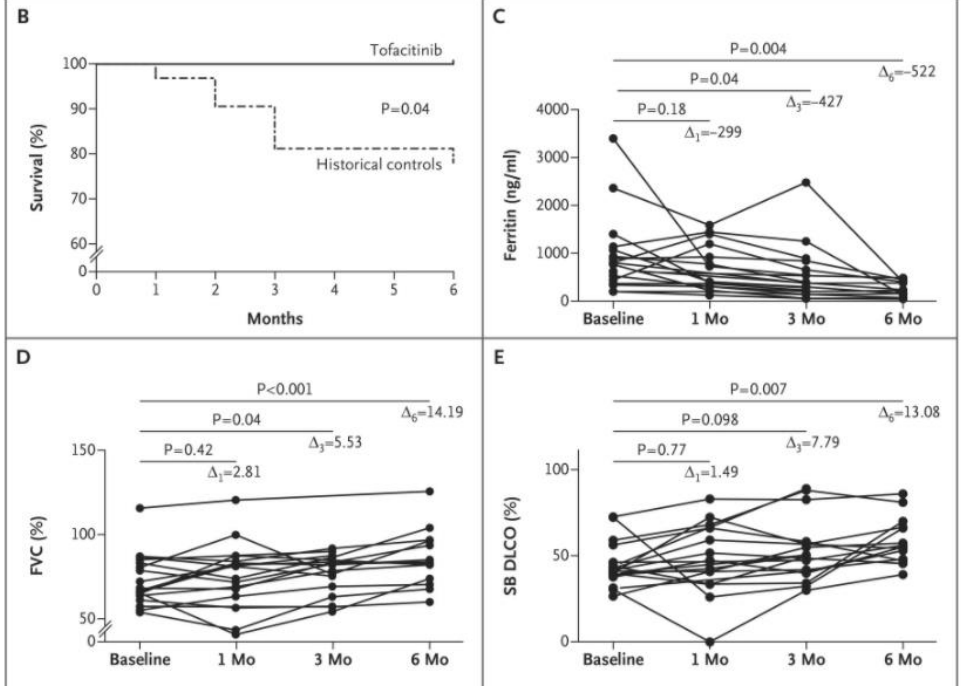
- If MDA 5 and maybe other DM ILD has a interferon signature, is there a role for JAK inhibitor here?



A

	Tofacitinib (N=18)	Historical Controls (N=32)	P Value
Age — yr	47.6±13.8	52.5±10.6	0.16
Female sex — no. (%)	11 (61)	25 (78)	0.33
History of smoking — no. (%)	2 (11)	2 (6)	0.61
Duration of ILD — mo	1.4±0.7	1.7±1.3	0.45
FVC — % of predicted value	73.4±15.2	71.9±15.3	0.76
SB DLCO — %	44.8±12.8	47.3±16.1	0.59
High-resolution CT score	118.2±13.2	127.2±24.8	0.16
Ferritin level — ng/ml	936.9±798.1	737.8±631.6	0.34
Creatine kinase level — U/ml	86.7±98.2	50.6±43.5	0.09
Albumin level— g/liter	33.5±5.3	31.8±3.3	0.18
Lactate dehydrogenase level — IU/liter	362.8±294.4	317.5±149.0	0.49
ESR — mm/hr	31.0±19.0	29.9±21.1	0.85
Maximum dosage of glucocorticoid — mg/day	78.0±54.4	87.9±81.8	0.65
Exposure to immunosuppressant — no. (%)			
Cyclosporine	2 (11)	19 (59)	
Mycophenolate mofetil	1 (6)	6 (19)	
Cyclophosphamide	0	2 (6)	
Azathioprine	0	1 (3)	
Exposure to pirfenidone — no. (%)	1 (6)	12 (38)	0.02

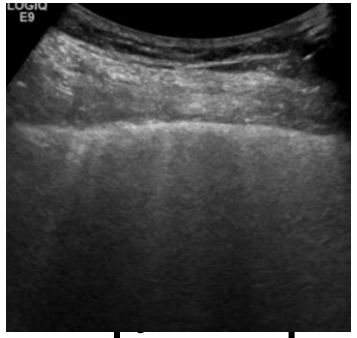


[Chen et al Tofacininib in Amyopathic ILD DM](#)
[July 18, 2019](#)
N Engl J Med 2019; 381:291-293
DOI: 10.1056/NEJMc1900045

Comments:
Again, small study
Historic controls

Screening 2022 for CTD ILD: there may be more than one way to do this

- HRCT
- Serial PFTs
- In office US
- Electronic stethoscope (?)
- Home monitoring devices i.e. ambulatory saturation etc.



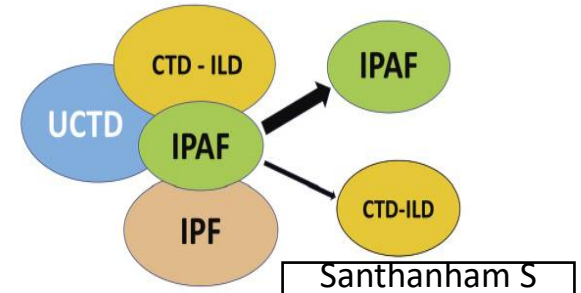
How aggressive to screen in CTD for ILD and whom?

- **Scleroderma**:HRCT at baseline, and Echo/PFTs baseline then PFT yearly (>10% decline in FVC or composite FVC/DLCO decline with assessment of extent fibrosis on CT)
- **IIM**: Baseline PFT/CT ,especially in antisynthetase patients/MDA5.
- **MDA 5** : frequent PFTs q 3-6 months esp the first 1-2 years
- **RA**: probably a risk factor analysis in combination with a functional test and emerging genetic and other biomarkers will determine who gets PFT/CT scanning or screen using a low dose CT in those who qualify for lung cancer screening. Many active efforts at numerous institutions to find these patients.

IPAF designation (Fischer A et al EJR 2015)

A. Clinical domain	B. Serologic domain	C. Morphologic domain
1. Distal digital fissuring (mechanic hands) 2. Distal digital tip ulceration 3. Inflammatory arthritis or polyarticular morning joint stiffness >60 min 4. Palmar telangiectasia 5. Raynaud's phenomenon 6. Unexplained digital oedema 7. Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)	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 . Anti-Smith . Anti-topoisomerase (Scl-70) 0. Anti-tRNA synthetase (e.g., Jo-1, PL-7, PL-12; thers are: EJ, OJ, KS, Zo, tRS) 1. Anti-PM-Scl 2. Anti-MDA-5	1. Suggestive radiology patterns by high-resolution computed tomography (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. Multi-compartment involvement (in addition to interstitial pneumonia): a) Unexplained pleural effusion or thickening b) Unexplained pericardial effusion or thickening c) Unexplained intrinsic airways disease d) Unexplained pulmonary vasculopathy

ANA, antinuclear antibody; HRCT, high-resolution computed tomography; IPAF, interstitial pneumonia with autoimmune features; LIP, lymphoid interstitial pneumonia; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; PFT, pulmonary function testing.



Santhanham S 2020

UCTD – Undifferentiated connective tissue disease; IPAF – Interstitial pneumonia with autoimmune features; IPF – Idiopathic pulmonary fibrosis; CTD – ILD – Connective tissue disorder associated interstitial lung disease

Summary Slide

- ILD associated with CTD can have a mortality that rivals IPF
- Risk factors for ILD in different population of CTD are identifiable
- Inflammatory disease can be treated with anti-inflammatory agent and emerging data suggests that fibrotic disease may be amenable to treatments employed in IPF
- Early identification of those at risk and frequent monitoring is important to avoid progression of disease and missed opportunity for treatment, clinical trials and if needed lung transplant.

Review Question 1

- Which of the following antibodies is associated with ILD in the rheumatic diseases?
- A Scl-70
- B Ro antibody
- C PL-12
- D MDA 5 antibody
- D A, C and D
- E all of the above

The correct answer is E

- Scl-70 or topoisomerase antibody positive patients are at highest risk for ILD in systemic sclerosis
- Ro antibody can be seen in those patients with scleroderma like syndromes with ILD, Sjogren with ILD and also Ro antibody + in association with antisynthetase antibodies.
- PL-12 antibody is seen in the antisynthetase syndrome. PL-12 + patients have a high risk for ILD
- MDA 5 anibody is part of a clinical syndrome involving the skin, sometimes inflammatory myositis and potentially rapidly progressive ILD.

Review Question 2

- A 30 year old healthy female never smoker presents with progressive dyspnea, low grade fever, and fatigue over the prior 3 months. No known occupational or home exposures to mold or dust. She has mechanics hands, and normal muscle and joint examination. HIV negative, CBC ,CK and Aldolase are normal . FVC % predicted is 70% and DLCO is 68% corrected for hemoglobin. A HRCT shows features of organizing pneumonia and NSIP. Ro52 ab is + and a myositis panel is pending. What is the best diagnostic and therapeutic approach in this patient ?
- A Begin steroids high dose, consider either MMF or Rituxan and await myositis panel
- B. Perform a bronchoscopy now
- C Perform a lung biopsy now
- D order the MDA 5 antibody and begin steroids and Rituxan

The best answer is A

- This clinical scenario is most consistent with the antisynthetase syndrome. Jo-1 is the most common antibody identified in this syndrome but others include Pl-7,PL-12 amongst others. A portion of such patients will also be Ro52 antibody positive as well. If this pt is antisynthetase ab + we would in most cases not do a lung biopsy unless there was evidence to suggest an alternative or additional diagnosis like malignancy.
- A bronchoscopy is useful if infection or granulomatous disease is suspected , neither of which appear likely in this case.
- The MDA 5 syndrome is possible here , given the ILD and even mechanics hands which have been seen, but the most likely diagnosis is antisynthetase syndrome. The choice of DMARD or biologic agent to add to steroids in this case is unclear though in severe or rapidly progressive cases Rituxan or cyclophosphamide are both options.

Summary/Take Home Slide

- ILD associated with CTD can have a mortality that rivals IPF
- Risk factors for ILD in different population of CTD are identifiable
- Inflammatory lung disease like in dermatomyositis can be treated with anti-inflammatory agent and emerging data suggests that fibrotic disease may be amenable to treatments employed in IPF
- Early identification of those at risk and frequent monitoring is important to limit progression of disease and avoid a missed opportunity for treatment, clinical trials and if needed lung transplant.
- A multidisciplinary approach can aid in optimizing diagnosis and treatment.

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