

Interstitial Pneumonia With Autoimmune Features: The first 11 years.

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Disclosures

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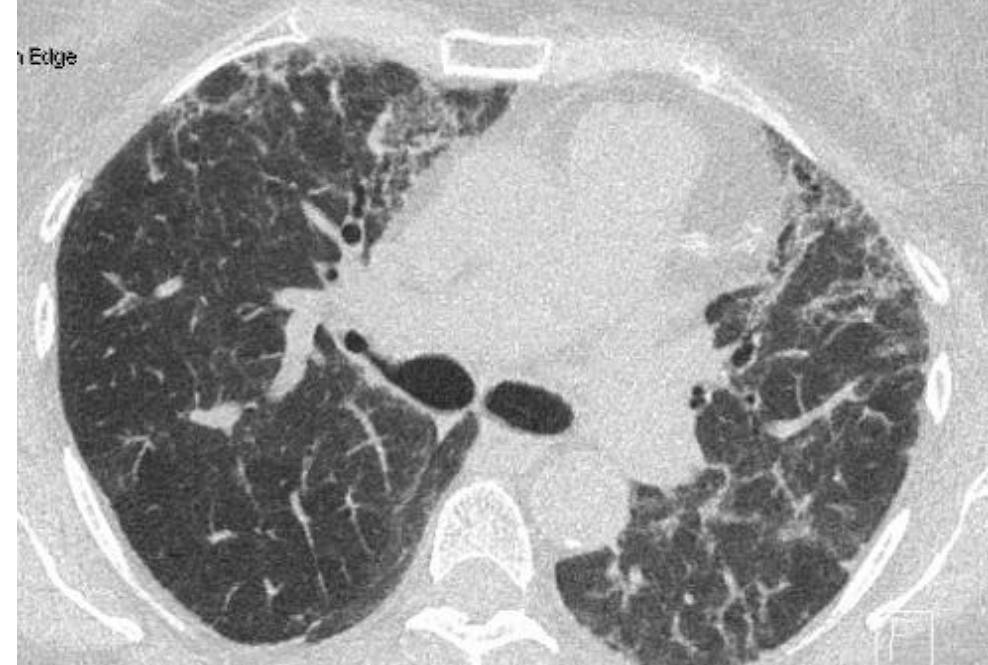
Case Presentation

65 year old female presented to establish care after moving to Richmond

Diagnosed with “pulmonary fibrosis” in 2014- progressively worse in 2017

Seen by pulmonology in Northern Virginia

- ✓ No definite exposures
- ✓ Raynaud’s present for 5 years but no other autoimmune symptoms
- ✓ No family history of interstitial lung disease/ premature graying
- ✓ Laboratory workup: ANA (+) 1:320- rest is negative. Myomarker panel positive for Ro-52 antibodies
- ✓ Pulmonary Function Tests: spirometry suggestive of severe restriction and severe reduction in DLCO
- ✓ Required 3lt via NC on exertion, no need for oxygen at rest
- ✓ Echocardiogram with evidence of elevated right sided pressures- RHC verified the presence of severe pulmonary hypertension



Case Presentation

Referred for EBUS-TBNA: inconclusive

Referred for a surgical lung biopsy:

- Cellular and fibrosing NSIP
- Lymphocytic infiltrates and lymphocytic aggregates with germinal centers
- Foci of organizing pneumonia with Mason bodies
- Chronic pleuritis

Seen by rheumatology and she was told she had no evidence of systemic autoimmune disease

Interstitial Lung
Disease

Pulmonary
Hypertension

What is wrong with this patient?

+ ANA
+ anti- Ro52

Raynaud's

NSIP
Organizing Pneumonia
Germinal centers

What is your diagnosis?

Many patients have an autoimmune “flavor” but no diagnosable systemic autoimmune disease

Names used to describe this phenotype

- ✓ Lung dominant Connective Tissue Disease
- ✓ Autoimmune featured ILD
- ✓ Undifferentiated Connective Tissue Disease associated ILD

Task Force on Undifferentiated Forms of CTD-ILD was formed

- ✓ 21 members: 13 pulmonologists/ 4 rheumatologists/ 3 thoracic radiologists/ 1 pathologist
- ✓ Multiple remote meetings
- ✓ 3 in person meetings



An official European Respiratory Society/ American Thoracic Society research statement: interstitial pneumonia with autoimmune features

- Descriptive term of the disease process
- Any reference to connective tissue disease was avoided
- The panel recognized that the criteria used may not be favored by everyone
- The statement was supposed to be a first draft that can be updated / revised in the future
- The term was not meant to guide clinical management or diagnostic testing but to facilitate the more thorough investigation of this population

Interstitial Pneumonia with Autoimmune Features

1. Interstitial lung disease **must be** present (imaging or pathology)
2. **No identifiable etiology** for the interstitial lung disease
3. Criteria for a classifiable systemic autoimmune rheumatic disease **must not be present**
4. At least 2 of the following criteria should be met
 - ✓ Clinical Domain
 - ✓ Serologic Domain
 - ✓ Morphologic domain

Criteria- Clinical Domain

- ✓ Mechanic Hands
- ✓ Digital tip ulceration
- ✓ Inflammatory arthritis or polyarticular stiffness
- ✓ Palmar telangiectasias
- ✓ Raynaud's phenomenon
- ✓ Unexplained digital edema
- ✓ Gottron's sign



Criteria- Serologic Domain

- ✓ ANA at $\geq 1:320$ or ANA nucleolar or centromere pattern at any titer
- ✓ Rheumatoid factor ≥ 2 times the upper limit of normal
- ✓ Anti-CCP
- ✓ Anti-dsDNA
- ✓ Anti-Ro
- ✓ Anti-La
- ✓ Anti-ribonucleoprotein
- ✓ Anti-Smith
- ✓ Anti-topoisomerase
- ✓ Anti-tRNA synthetase (Jo-1, PL-7, PL-12, EJ, OJ, KS, Zo)
- ✓ Anti-PM/Scl
- ✓ Anti-MDA-5

Criteria- Morphologic Domain

Imaging Patterns

NSIP
Organizing Pneumonia
NSIP/ OP overlap
Lymphocytic Interstitial
Pneumonia

Histopathology Patterns

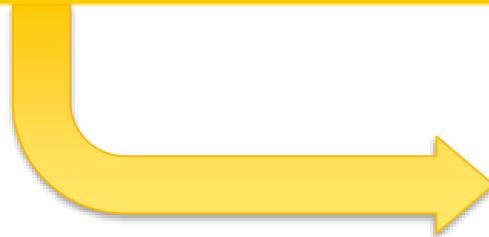
NSIP
Organizing Pneumonia
NSIP/ OP overlap
Lymphocytic Interstitial Pneumonia
Germinal Centers
Diffuse lymphoplasmacytic Infiltrates

Multi-Compartment Involvement

Unexplained pleural effusion or thickening
Unexplained pericardial effusion or thickening
Unexplained airways disease
Unexplained pulmonary vasculopathy

Back to our case

- ✓ Interstitial Lung Disease
- ✓ No etiology for the imaging abnormalities
- ✓ No rheumatologic disease present
- ✓ Other criteria
 - Clinical criterion met – Raynaud's
 - Serologic criterion met- ANA at 1:320 and positive anti-Ro52
 - Morphologic criteria met- NSIP pattern + germinal centers + multi-compartment involvement



Fulfills IPAF Criteria

Epidemiology and Presentation

Epidemiology

10-20% of patients in ILD registries
14% of ILD patients at VCU
Female predominance 60/40
Median age 50-60
Up to 60% with tobacco use history

Clinical Presentation

Dyspnea and cough
Raynaud's and Inflammatory arthritis
ANA positivity in 80% of cases
NSIP the most common imaging pattern

Diagnostic Journey

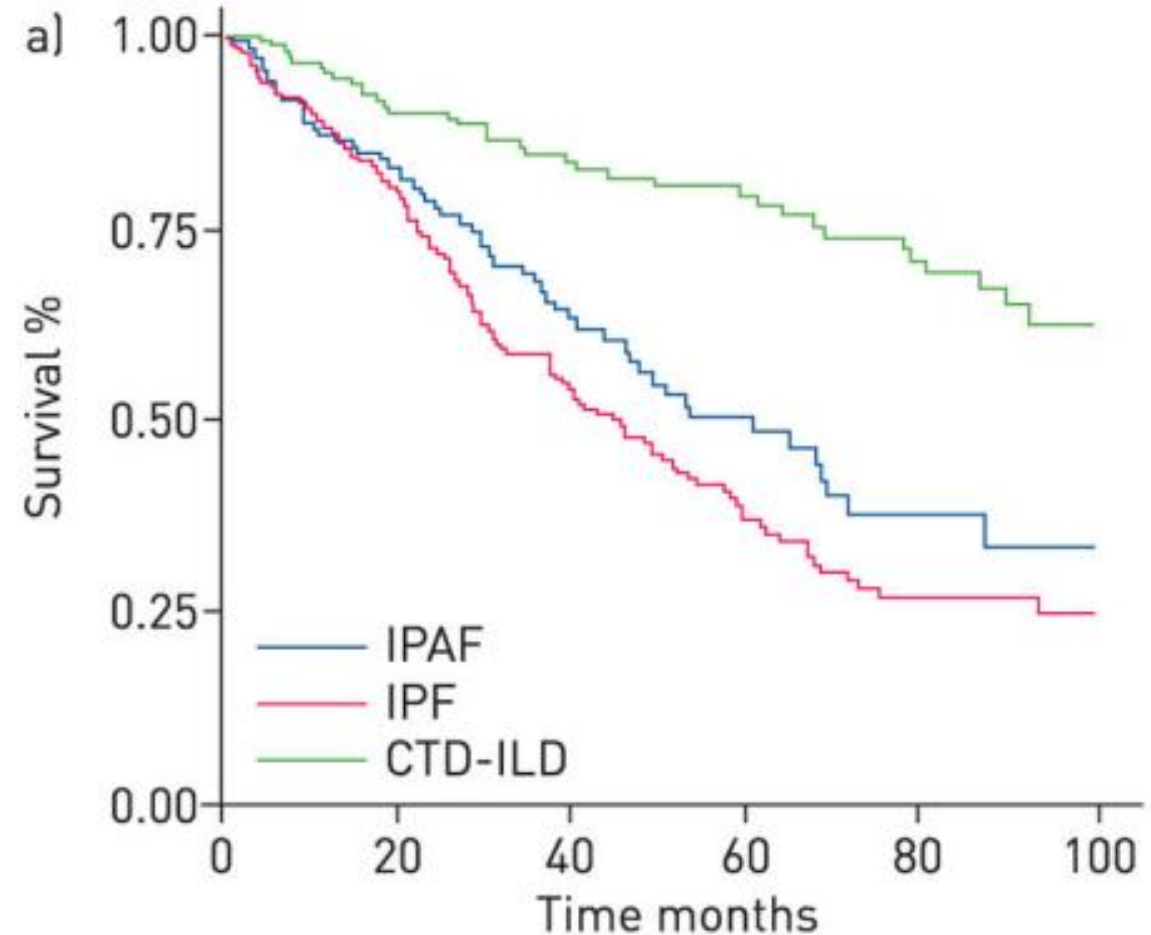
25% of patients fulfill 3/3 criteria
Up to 50% do not fulfill clinical domain
30% will undergo a lung biopsy
Evolving role for cryobiopsy

Pathophysiology

- Very limited data given the heterogeneity of the condition
- Evidence of epithelial cell dysfunction (elevated KL-6, SPA, SPD levels)
- Inflammatory activation (increased CXCL9, 10, 11)
- Fibrotic pathways (activated fibrocytes identified in patients with IPAF)
- Contribution from genetic factors (MUC5B, short telomeres)

Prognosis

- ✓ Varies considerably from series to series
- ✓ Generally better than IPF
- ✓ Slightly worse than SARD-ILD
- ✓ Predictors of poor outcome
 - Advanced age
 - Active smoking
 - Reduced exercise capacity
 - Reduced baseline spirometry
 - Elevated KL-6 levels



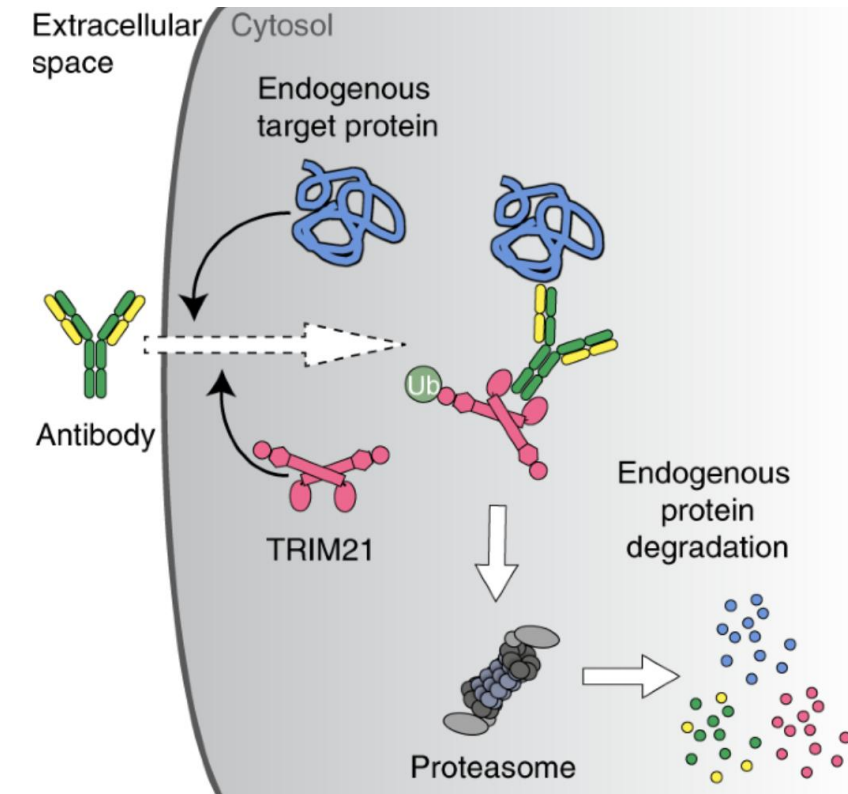
Oldham et al, Eur Respir J 2016
Dai et al, Clin Rheumatol 2018
Vahidi et al, Respir Med 2024

Anti-Ro52 antibodies- an enemy from within

- Part of the SSA antibody (Ro52 + Ro60)
- Myositis – associated antibody
- Target TRIM (Ro52) protein
- **Present in 30% of IPAF patients**
- 50% of patients with Ro52 positivity and ILD fulfill IPAF criteria

TRIM protein function

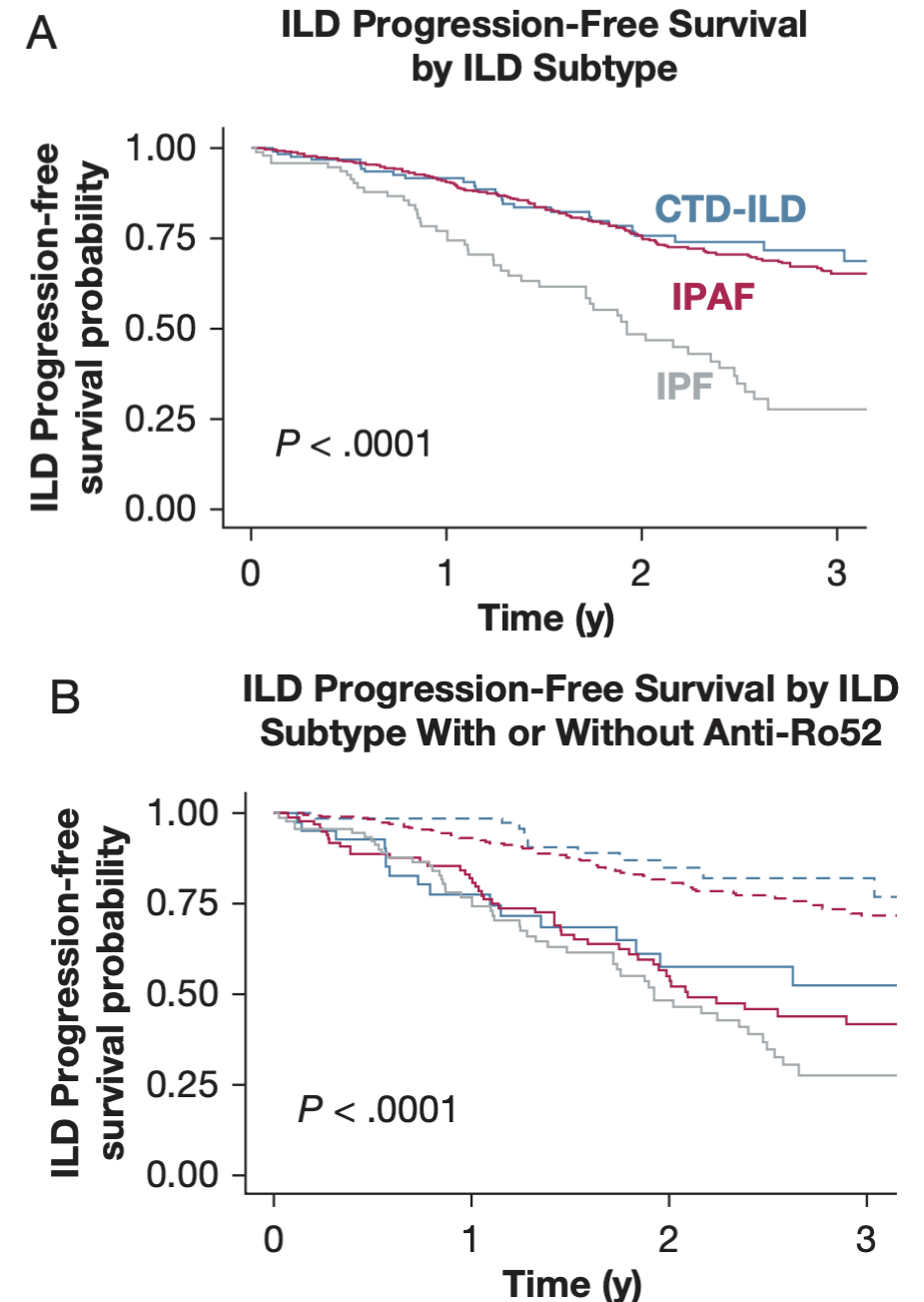
- Intracellular pathogen/ virus defense
- Immune regulation
- Metabolic regulator



Anti-Ro52 as a prognostic factor in IPAF

Anti-Ro52 positivity associated with

- ✓ Increased progression risk
- ✓ Increased hospitalization risk
- ✓ Increased mortality risk



Imaging Features and Outcomes

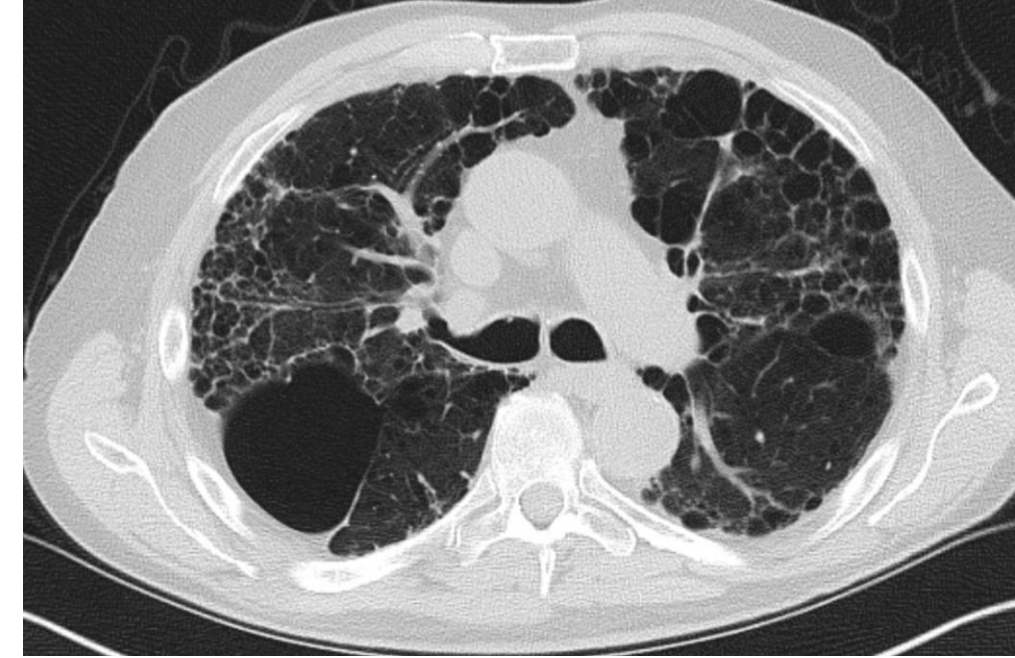
Imaging is the strongest predictor for disease behavior

Main patterns:

- ✓ Usual Interstitial Pneumonia
- ✓ Non-specific Interstitial Pneumonia
- ✓ Organizing Pneumonia

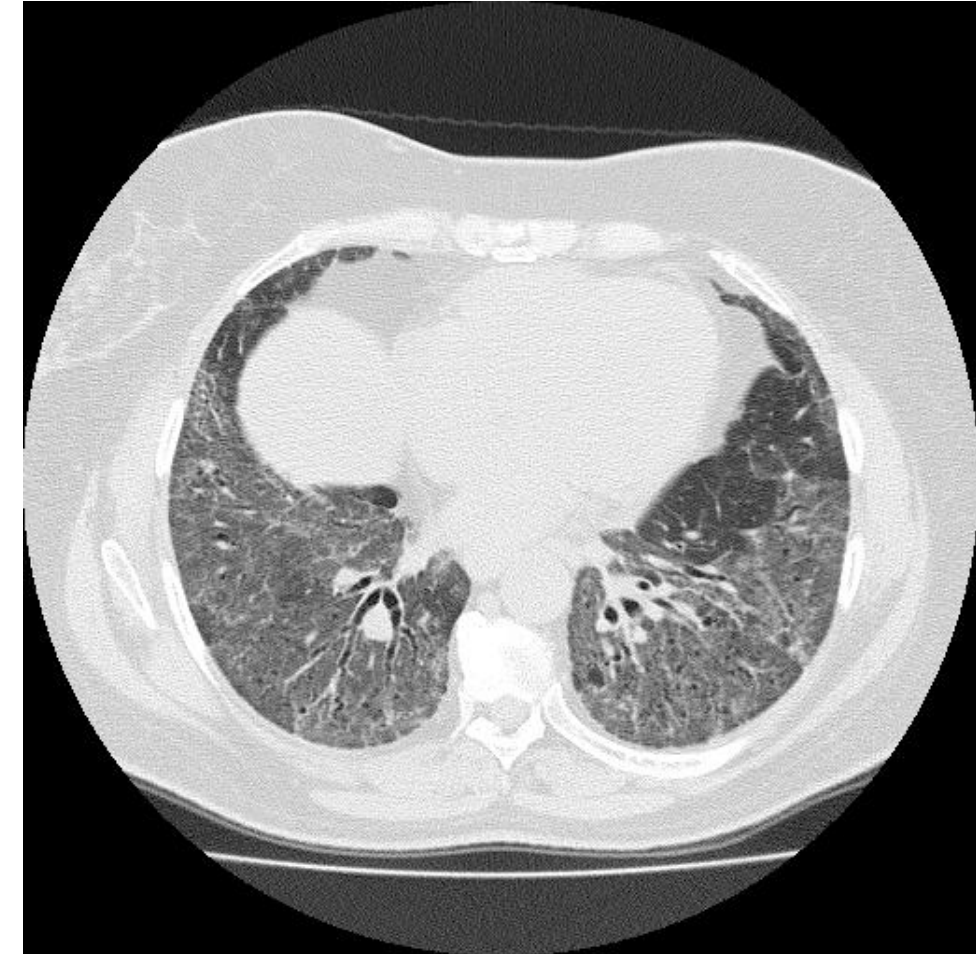
Usual Interstitial Pneumonia

- ✓ Fibrotic pattern –minimal inflammation
- ✓ Most common pattern associated with IPF
- ✓ Lower lobe predominant
- ✓ Peripheral
- ✓ Reticulations but little (if any) ground glass
- ✓ Traction bronchiectasis
- ✓ Honeycombing



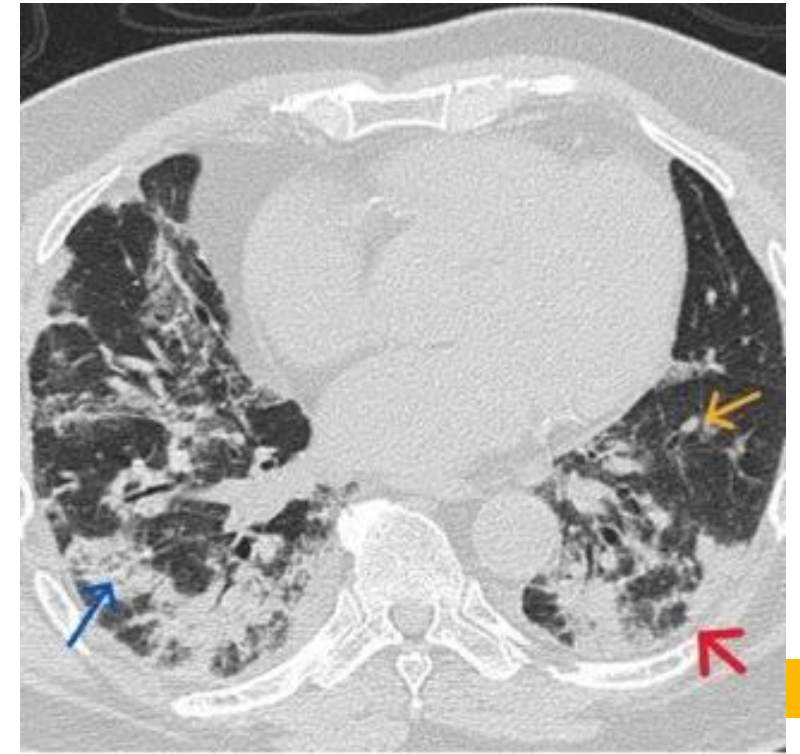
Non- specific Interstitial Pneumonia

- ✓ The most common pattern associated with SARD
- ✓ Lower lobe predominant
- ✓ Central and peripheral
- ✓ Ground glass opacities
- ✓ Reticulations and traction bronchiectasis may be present
- ✓ Honeycombing usually absent
- ✓ Subpleural sparing present



Organizing Pneumonia

- ✓ May coexist with NSIP
- ✓ Consolidations
- ✓ Air bronchograms
- ✓ Lower lobe predominant
- ✓ Usually peripheral



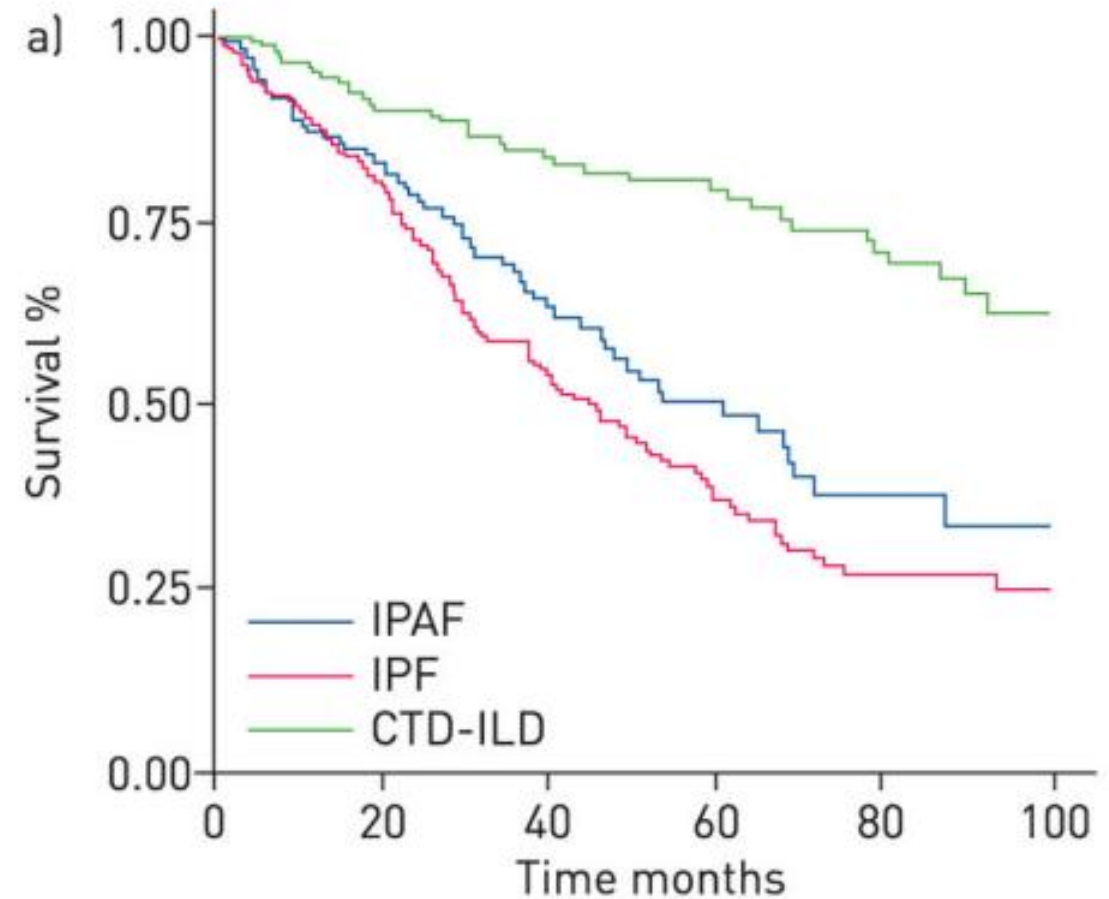
Imaging and Prognosis

Fibrosis → Worse outcomes

UIP pattern on imaging

- ✓ Worse short- term prognosis
- ✓ Accelerate rate of lung function decline
- ✓ Increased morbidity
- ✓ Explains the variability in mortality among IPAF cohorts

Organizing pneumonia on imaging is associated with better outcomes



Management

Disclaimer

- ✓ This population has not been studied specifically in prospective trials
- ✓ No official guidelines exist

But:

- ✓ Patients with IPAF have been included in some landmark studies
- ✓ Retrospective data are available
- ✓ Patients need to be treated now while waiting for the higher quality data

Immunosuppression in patients with IPAF

- ✓ Most patients on treatment are on immunosuppression
- ✓ Corticosteroids +/- DMARDs

Mycophenolate

- ✓ Less risk for progression in the first year of therapy
- ✓ Stabilization of FVC(%) and DLCO(%)
- ✓ Good tolerance profile

Cyclophosphamide

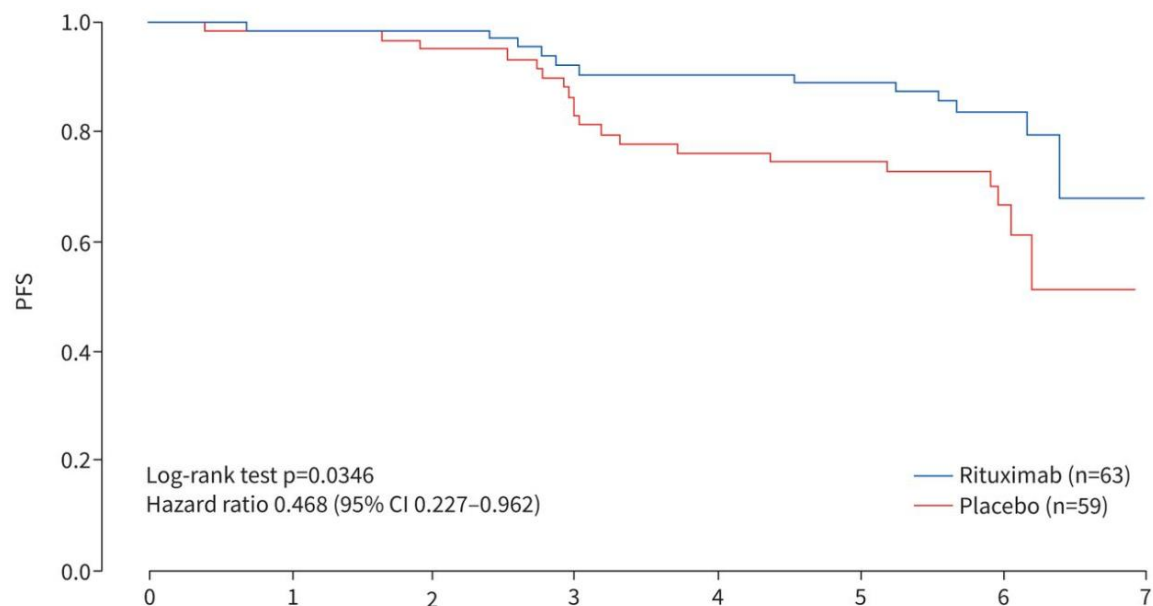
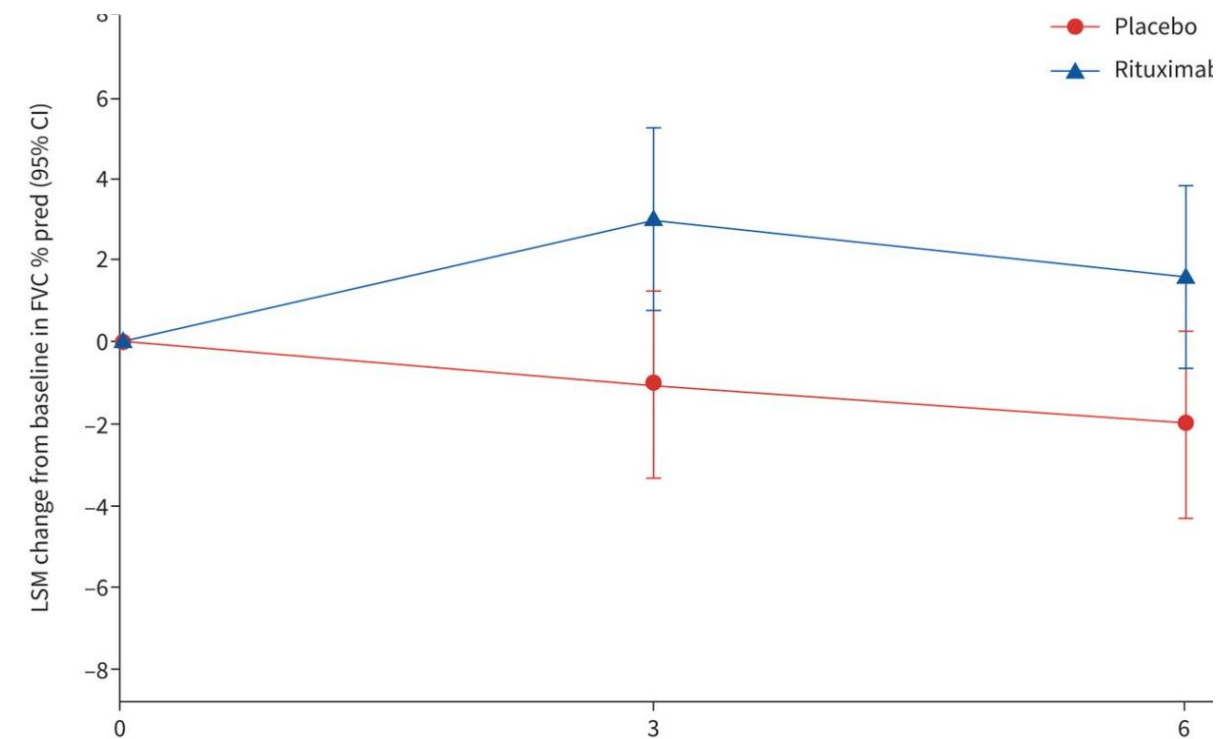
- ✓ Retrospective data suggest effectiveness in refractory disease
- ✓ Unfavorable side effect profile

Minimal to no data
on azathioprine,
tacrolimus or
biologics beyond
rituximab

The EVER-ILD experience

- **Inclusion criteria:** adult patients with SARD-ILD, IPAF or iILD with an NSIP pattern
- **Exclusion criteria:** UIP pattern on imaging/ pathology, RHC verified PH
- **Intervention:** rituximab + mycophenolate (2g/day) vs mycophenolate + placebo
- **Duration:** 6 months
- **Outcomes:** change in FVC (primary), PFS, quality of life, cumulative corticosteroid dose

- **122 patients enrolled (63 RTX +59 placebo)**
- **114 patients attended the 6 month visit**
- **36 patients with IPAF (30%)**



Other Outcomes

Increased number of exacerbations in the placebo arm

- No effect on corticosteroid exposure
- No effect on 6 minute walk distance
- No effect on dyspnea or cough scores
- No effect on quality of life

Safety Outcomes

- Increased infection risk with RTX
- Infusion reactions were rare
- 4 deaths in the placebo arm , 3 in RTX

Antifibrotics in IPAF

- ✓ Some patients will progress while on anti-inflammatory agents
- ✓ Disease progression is associated with poor outcomes
- ✓ Antifibrotics are beneficial in patients with various progressive fibrotic conditions
- ✓ Use of antifibrotics was associated with a reduction in the risk for clinical worsening in the NEREA registry (20% of which had IPAF)
- ✓ **No antifibrotic has been studied specifically in patients fulfilling IPAF criteria**

Antifibrotic Medications

- ✓ Nintedanib – tyrosine kinase inhibitor
- ✓ Pirfenidone - ??
- ✓ Nerandomilast – PDE4B inhibitor

Nintedanib

INBUILD:

- 25% of participants had SARD-ILD but only 5 participants were classified as IPAF
- Improvement in the rate of FVC loss by about 58% vs placebo (-172mL/year vs -70mL/year)
- No difference in efficacy between UIP and non –UIP patterns
- Trend towards reduction in death/ exacerbations
- No patients were on azathioprine, mycophenolate, rituximab or more than 20mg of prednisone/day

SENSCIS

- Largest study to date in Systemic Sclerosis ILD
- 45% reduction in the rate of lung function decline compared to placebo (-93mL/year vs -52mL/year)
- Additive benefit with mycophenolate
- No impact on PROs or skin scores
- **No data (prospective or retrospective) in patients with IPAF**

Pirfenidone

RELIEF study

- Phase II study among patients with progressive fibrotic ILD
- 13% of individuals fulfilled IPAF criteria
- Reduction in FVC decline (-114 mL/year vs -36mL/year) did not reach statistical significance
- Study was prematurely discontinued because of poor recruitment
- Medication was well tolerated

Nerandomilast

FIBRONEER-ILD

- 28% of participants had SARD-ILD; unknown if any fulfilled IPAF
- 34% on baseline nintedanib therapy; no mycophenolate, rituximab or prednisone >15mg/day allowed
- Improvement in the rate of FVC loss by about 40% vs placebo (-107mL/year vs -62mL/year)
- Trend towards improvement in mortality/ hospitalizations/ death endpoint
- Results consistent regardless of baseline nintedanib use or imaging pattern
- Study evaluating the role of combining nerandomilast + immunosuppressive therapy currently enrolling
- **No data (prospective or retrospective) in patients with IPAF**

Non- pharmacological management

Pulmonary
Rehabilitation

Sleep study

Pulmonary
Hypertension
Evaluation

Supplemental
Oxygen



Lung
Transplantation
Evaluation

Palliative Care

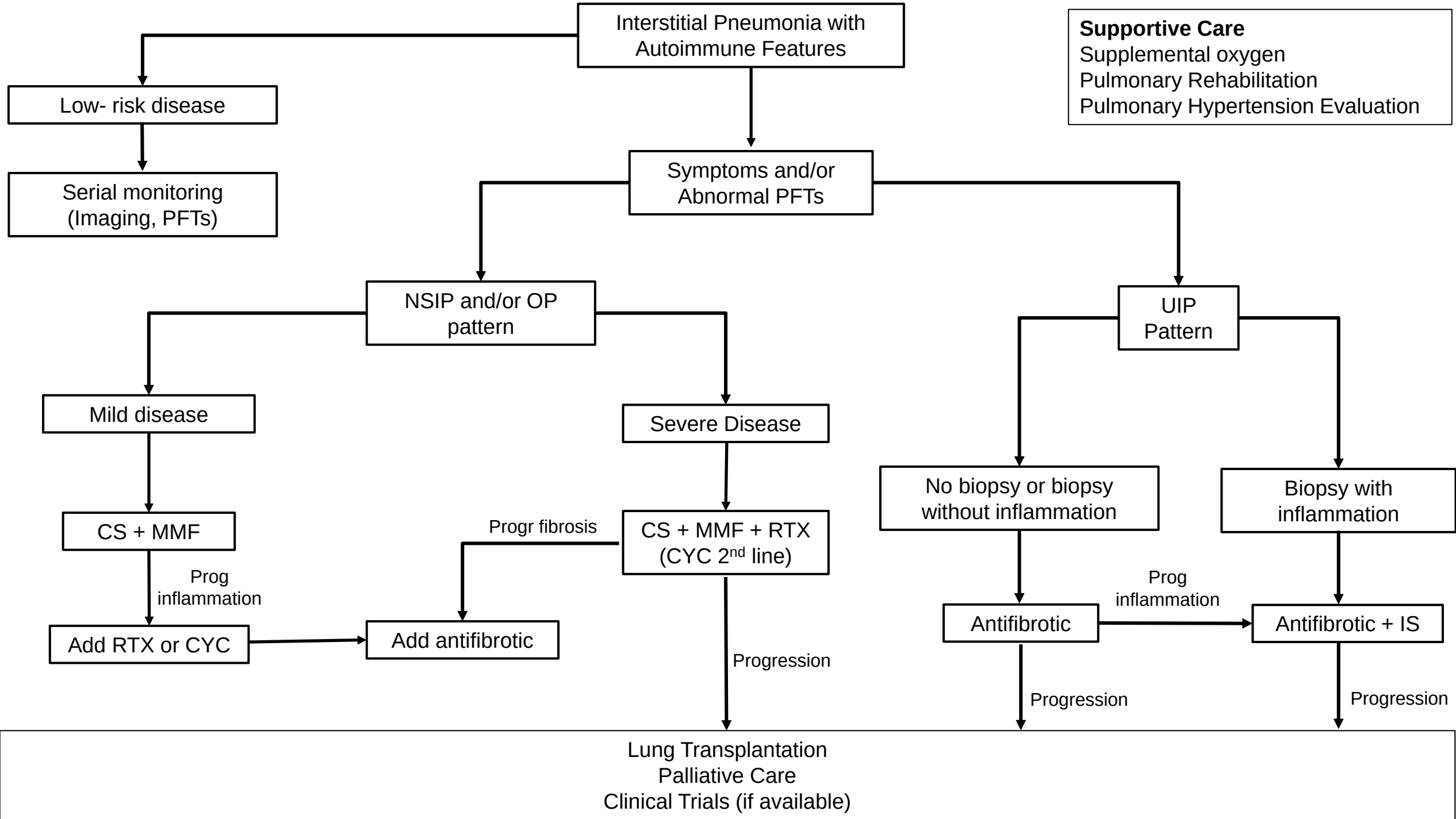
Lung transplantation

When to think about a lung transplant

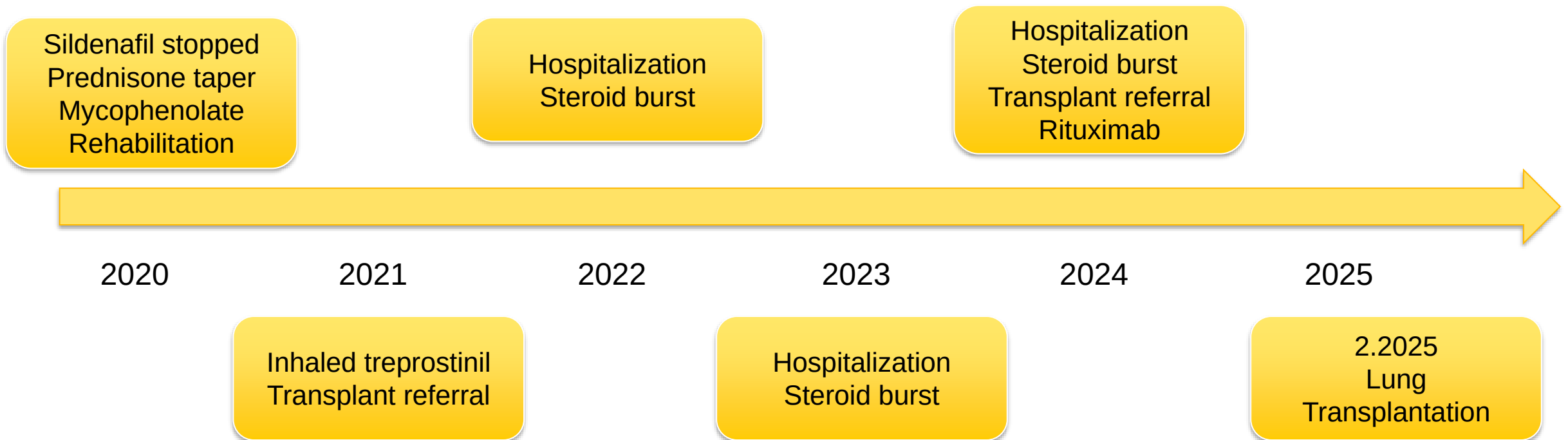
- **Aggressive disease**
- **Progressive disease**
- **Oxygen need at rest or exertion**

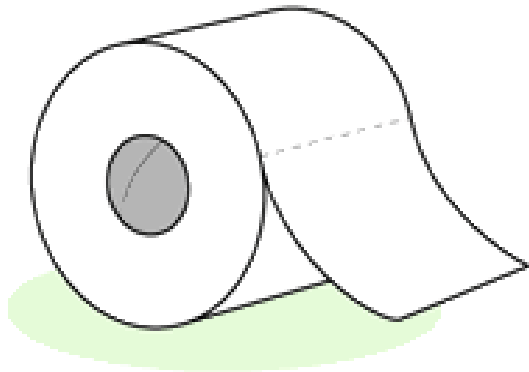
IPAF and Lung Transplantation

- Limited experience
- Similar criteria for referral and transplantation as patients with restrictive lung disease
- Should be considered for patients with advanced disease and no contraindications
- When performed in carefully selected candidates, lung transplantation is associated with outcomes similar to that of other restrictive conditions

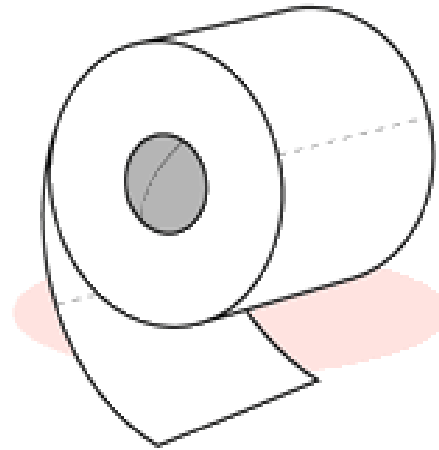


Back to our case....





This is right.
(good)



This is wrong.
(bad)

Controversies and Unanswered Questions

Is IPAF SARD-ILD in disguise?

Argument held since the entity was developed

Similarities

- ✓ Demographics
- ✓ Imaging
- ✓ Serologies

But.....

- ✓ Most will never receive SARD diagnosis
- ✓ Differences in pathophysiology
- ✓ Differences in prognosis

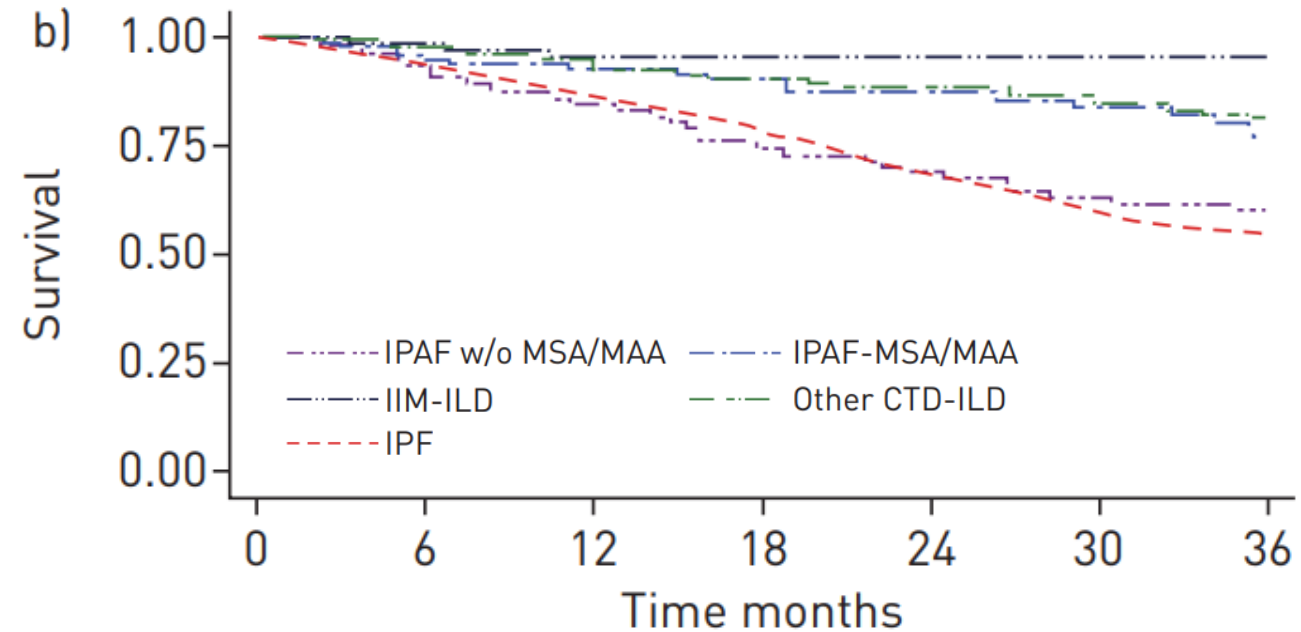


IPAF and evolution into SARD

- **How often does IPAF become “SARD-ILD”?**
 - ✓ 10-15% of IPAF patients will develop a classifiable SARD in the first 3 years since diagnosis
 - ✓ Longer follow up studies have reported conversion rates in up to 25% of cases
- **Predictors of future SARD Diagnosis**
 - ✓ Younger age at diagnosis
 - ✓ Female gender
 - ✓ Antibody profile (ant-Scl-70, anti-PM/Scl, anti-SSA, antisynthetase antibody)
 - ✓ Mechanic hands
 - ✓ Organizing pneumonia pattern on imaging/ pathology
 - ✓ *No treatment at the time of IPAF diagnosis?*

What about patients with positive myositis specific antibodies?

- ✓ Higher probability of receiving a formal SARD-ILD diagnosis
- ✓ Higher prevalence of organizing pneumonia
- ✓ Higher prevalence of organizing pneumonia/ NSIP overlap
- ✓ Better prognosis than the rest of IPAF
- ✓ Less severe ILD
- ✓ Response to immunosuppression



What about patients with ILD and ANCA positivity?

Currently ANCA is not part of the serologic criteria for IPAF

ANCA positive ILD

- ✓ Only a minority will develop vasculitis
- ✓ UIP is the most common pattern
- ✓ Pathology with UIP pattern + lymphocytic inflammation, lymphocytic aggregates and pleuritis
- ✓ Outcomes are slightly better than IPF but worse than SARD-ILD



Antinuclear antibodies

- ✓ A reduction in the required ANA titer to 1:160 has been proposed
- ✓ This may increase the rate of false positives unless specific ANA patterns are required

Pulmonary Vasculopathy

- ✓ Lacks specificity
- ✓ Indirect methods for estimating vascular disease are unreliable
- ✓ "Out of proportion" disease?

"Small airways disease"

- ✓ Common among all fibrotic ILDs
- ✓ This can also be seen in those with pre-existing asthma or COPD
- ✓ Few patients will have surgical biopsy

Criteria- Serologic Domain

- ✓ ANA at $\geq 1:320$ or ANA nucleolar or centromere pattern at any titer
- ✓ Rheumatoid factor ≥ 2 times the upper limit of normal
- ✓ Anti-CCP
- ✓ Anti-dsDNA
- ✓ Anti-Ro
- ✓ Anti-La
- ✓ Anti-ribonucleoprotein
- ✓ Anti-Smith
- ✓ Anti-topoisomerase
- ~~✓ Anti-tRNA synthetase (Jo-1, PL-7, PL-12, EJ, OJ, KS, Zo)~~
- ✓ Anti-PM/Scl
- ~~✓ Anti-MDA-5~~



+ ANCA

Criteria- Morphologic Domain

Imaging Patterns

NSIP
Organizing Pneumonia
NSIP/ OP overlap
LIP

Histopathology Patterns

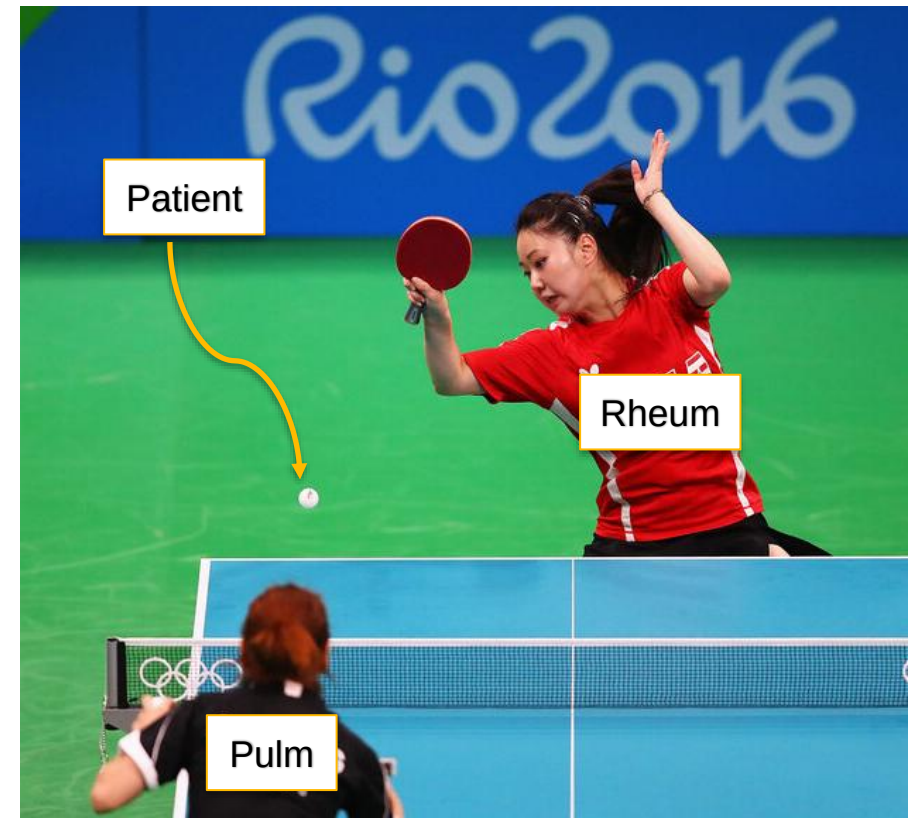
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Germinal Centers
Diffuse lymphoplasmacytic Infiltrates

Multi-Compartment Involvement

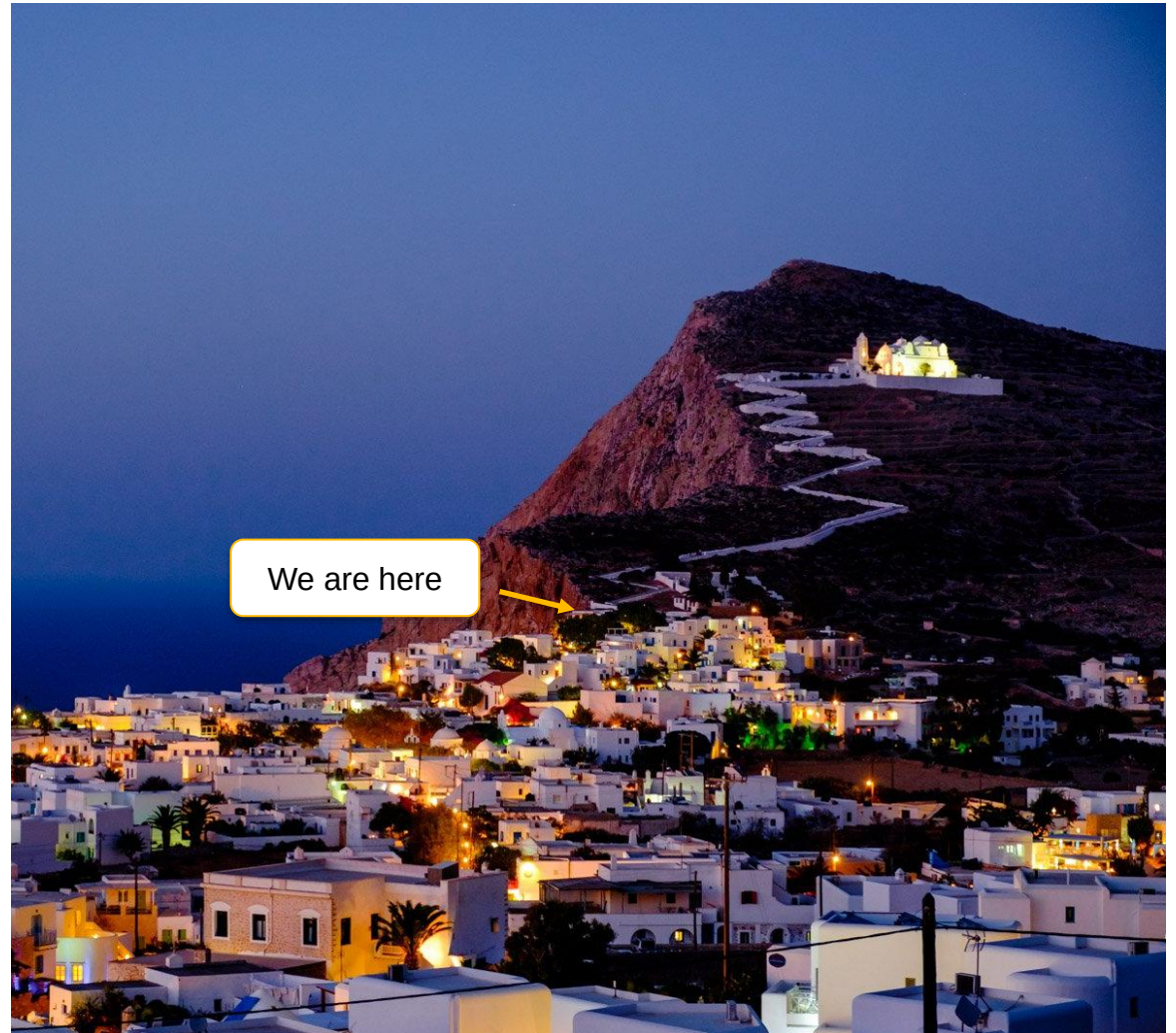
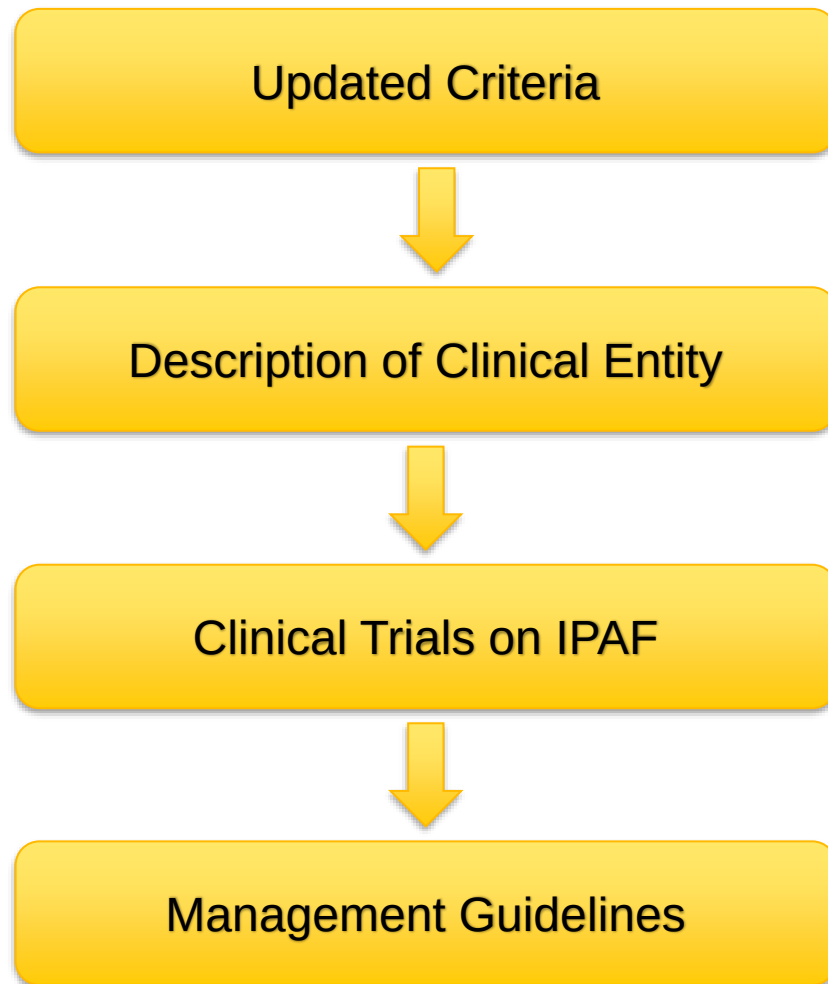
Unexplained pleural effusion or thickening
Unexplained pericardial effusion or thickening
~~Unexplained airways disease~~
~~Unexplained pulmonary vasculopathy~~
Out of proportion pulmonary hypertension

A critical appraisal

- **The Task Force on Undifferentiated Forms of CTD-ILD achieved its goals**
- IPAF is still a work in progress, but in the last decade
 - ✓ Triggered debate and discussion among specialists
 - ✓ Encouraged collaboration among disciplines
 - ✓ Stimulated research into the epidemiology and pathophysiology of the entity
 - ✓ Attracted attention to a population that was being neglected in the past



Next steps



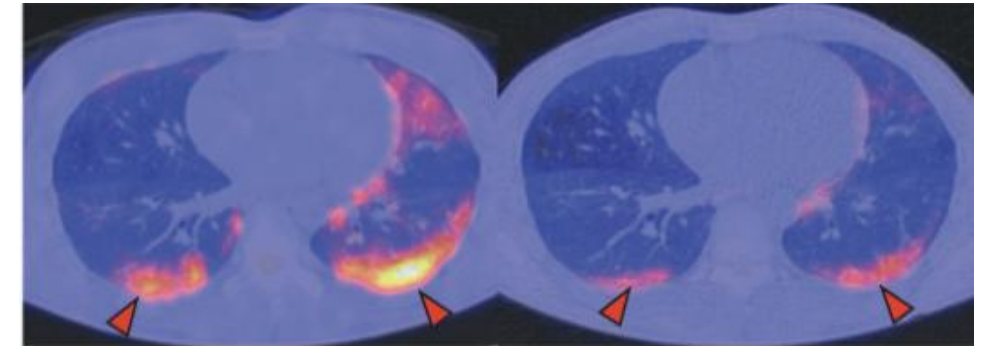
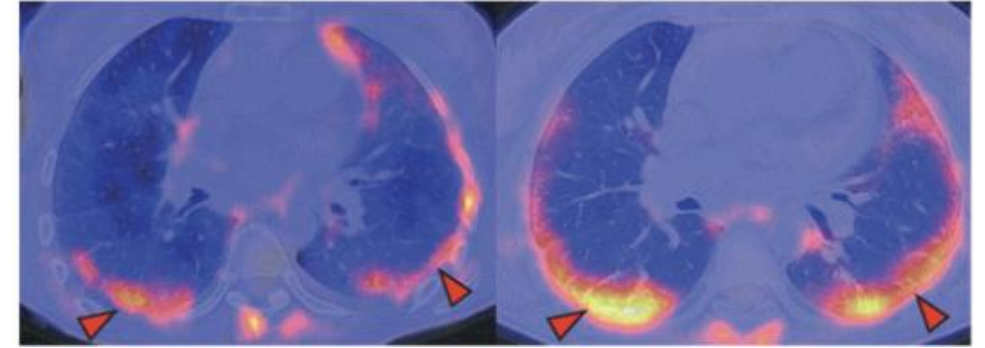
Future Developments

Better Classification using –omics approaches

- ✓ Imaging analysis (radiomics)
- ✓ Molecular profiling (proteomics)
- ✓ Genetic profiling (genomics)
- ✓ Metabolic profiling (metabolomics)

Better Prognostication

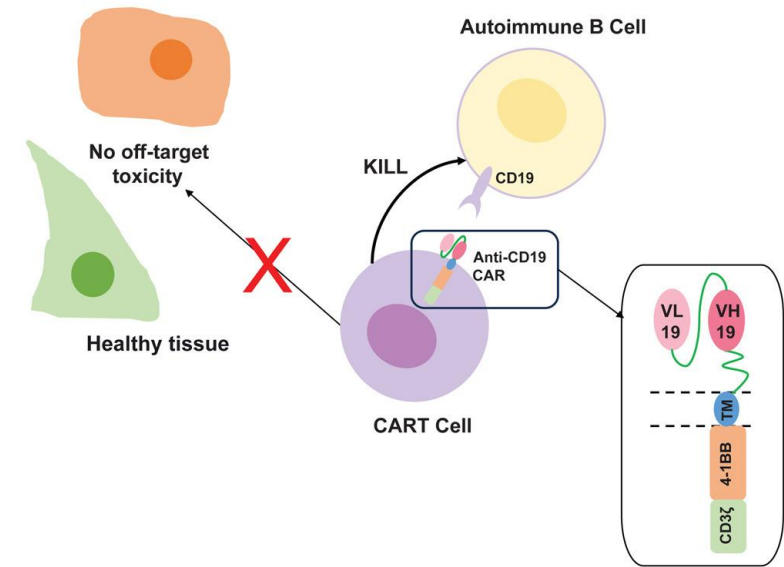
- ✓ Functional imaging
- ✓ -Omics approaches
- ✓ Real time response to treatment assessment



Future Developments

Treatment

- ✓ Upfront combination anti-inflammatory and antifibrotic therapies
- ✓ Expansion of the role of antifibrotics beyond the progressive fibrotic phenotype
- ✓ Further investigation of the role of biologics (beyond rituximab)
- ✓ CAR-T cell therapies
- ✓ Bispecific antibodies



Thank you!

