Pulmonary Involvement in Rheumatic Diseases
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Disclosures

Consultant for Abbvie, Amgen, Eli Lilly, Novartis

Clinical Trials for Abbvie, Amgen, Eli Lilly, GSK, Novartis, Pfizer, UCB

Speakers Bureau for Abbvie, Alexion, Amgen, Eli Lilly, Exagen, GSK, Novartis, Pfizer, Radius Health, UCB

Stocks none
• ILD refers to a heterogeneous collection of more than one hundred distinct lung disorders that tend to be grouped together because they share clinical, radiographic, and pathologic features.

• These disorders are sometimes called diffuse parenchymal lung disease (DPLD) to make the point that the interstitium is not the only compartment of the lung affected.
CLASSIFICATION

Several classification schemes for ILD have been proposed.

- Histopathologic &
- Clinical characteristics
- American Thoracic Society (ATS)/European Respiratory Society (ERS) consensus panel classification system (2001)
Interstitial lung disease

Etiology known

Inorganic exposure
- Asbestos
- Silica
- Hard metals
- Coal dust

Organic exposure
- Birds
- Hay
- Mold
- Mycobacteria

Smoking
- DIP
- RB-ILD
- LCH

Rare forms of ILD
- LAM
- Vasculitis

Granulomatous
- Sarcoidosis

Connective tissue disease
- Rheumatoid arthritis
- Polymyositis/dermatomyositis
- Scleroderma
- Sjögren syndrome

Etiology unknown

Idiopathic interstitial pneumonias
- IPF
- Non-IPF

NSIP
- COP
- LIP
- AIP
Clinical History

• Typical presentation of ILD - nonspecific
• Dyspnea on exertion or cough & abnormal radiograph.
• Symptoms are usually progressive.
• Two-thirds of patients with ILD are over 60 years of age at diagnosis.
• Women - LAM
Time Course of Disease Onset

- **Acute:**
  - Cryptogenic organizing pneumonia (COP)
  - Acute eosinophilic pneumonia (AEP)
  - Acute hypersensitivity pneumonitis
  - Diffuse alveolar hemorrhage
  - Acute interstitial pneumonia (AIP)
  - Acute exacerbation of idiopathic pulmonary fibrosis or other ILDs
• Subacute to Chronic
  • Connective tissue disease–associated ILD
  • Idiopathic pulmonary fibrosis (IPF)
  • Sarcoidosis
  • Chronic hypersensitivity pneumonitis (CHP)
  • Occupational lung disease
  • Nonspecific interstitial pneumonia (NSIP)
  • Desquamative interstitial pneumonitis (DIP)
  • Respiratory bronchiolitis interstitial lung disease (RB-ILD)
  • Lymphocytic interstitial pneumonia (LIP)
  • Chronic eosinophilic pneumonia (CEP)
h/o wheezing- hypersensitivity pneumonitis, eosinophilic pneumonia or sarcoidosis.

h/o pleuritic chest pain- serositis in a patient with CTD, or pneumothorax from LAM, LCH.

Hemoptysis- diffuse alveolar hemorrhage
Systemic Symptoms

Connective tissue disease is a frequent cause of ILD

nonspecific symptoms such as night sweats, fever, fatigue, or weight loss suggest an underlying inflammatory condition.
Dermatologic symptoms

Heliotrope rash
- Periorbital violaceous erythema with or without edema of eyelids and periorbital tissue.
- Highly characteristic of DM.

Dermatomyositis

Gottron’s papules, or “mechanic’s hands"
Rheumatoid Arthritis ILD

Recognized more frequently since HRCT scans of the lungs available

Majority of respiratory manifestations occur in the first 5 years of disease onset but respiratory symptoms may precede disease onset in 10-20%

ILD is the most common pulmonary manifestation detected in up to 60% of cases on HRCT but clinically significant in only 10%

RA-ILD occurs more frequently in men with male to female ratio 2:1

Additional risk factors include cigarette smoking, CCP positivity and RA disease activity

UIP pattern is most common in 8-66%, NSIP pattern in 19-57% and organizing pneumonia in 0-11%
UIP pattern predicts a worse survival (3.2 versus 6.6 years) when compared to those with non-UIP pattern and a similar survival to those with IPF.

The predominance of the UIP pattern contrasts with other CTDs such as SSC where the pathologic pattern found on lung biopsies is most commonly NSIP.

NSIP occurs in about 1/3 of patients and is associated with longer duration of articular manifestations, lower risk of disease progression and better treatment response.

TH-17 cytokines such as IL-17A and TGF beta cause fibrosis through direct effects on fibroblasts leading to their proliferation and extracellular matrix generation.
Airway disease can occur in up to 39-60% of cases. Cricoarytenoid joint involvement can lead to hoarseness and aspiration. Bronchiectasis as been demonstrated on HRCT in about 30% of RA cases but often is clinically silent. Constrictive bronchiolitis (or bronchiolitis obliterans BOOP) is rare.
Systemic sclerosis
ILD is common in patients with SSC with up to 90% of patients showing evidence of interstitial changes on HRCT and 40-75% have abnormalities on PFTs.

Risk factors include male gender, diffuse cutaneous SSC, anti-topoisomerase antibodies, cigarette smoking, ethnicity (Native American and African American).
• Systemic lupus erythematosus
• malar rash,
• photosensitivity skin reaction,
• hair loss
Gastrointestinal symptoms

- esophageal motility problems - systemic sclerosis and polymyositis
- Chronic, intermittent aspiration can lead to progressive fibrotic lung disease.
- bloating and diarrhea - inflammatory bowel disease
Musculoskeletal complaints

- Connective tissue disease—arthralgias, morning stiffness, joint swelling and erythema.
- Swollen fingers (“sausage digits”) may be observed in systemic sclerosis and polymyositis.
- Raynaud’s phenomenon—scleroderma, mixed CTD, SLE & antisynthetase syndrome.
Ophthalmologic symptoms

- DRY EYES - SJÖGREN SYNDROME
- H/O UVEITIS MAY HAVE SLE OR SARCOIDOSIS
Increasing edema, syncopal events, or exertional chest discomfort may indicate severe pulmonary hypertension.

Presence of palpitations or syncope in a patient with sarcoidosis - Cardiac sarcoidosis.

Pleuritic chest pain, leg swelling & increasing dyspnea - consideration of acute pulmonary embolism.
Prior diagnosis of connective tissue disease

Case of HIV disease- lymphocytic interstitial pneumonia (LIP) are common.

h/o acute or chronic kidney disease might suggest underlying vasculitis, pulmonary–renal syndromes, or CTD.

h/o liver disease could suggest sarcoidosis, primary biliary cirrhosis.
MEDICATION HISTORY

- Nitrofurantoin
- Amiodarone
- NSAIDs
- h/o recent chemotherapy
- h/o immune-modulating drug use
<table>
<thead>
<tr>
<th><strong>Antibiotics</strong></th>
<th><strong>Chemotherapeutic</strong></th>
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<tbody>
<tr>
<td>Nitrofurantoin</td>
<td>All-trans retinoic acid (ATRA)</td>
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<td>Minocycline</td>
<td>Alpha-interferon</td>
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<td>Cephalosporins</td>
<td>Antithymocyte globulin</td>
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<td>Carmustine (BCNU)</td>
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<td>Colony-stimulating factors (GM-CSF)</td>
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<td>Cyclophosphamide</td>
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<td>Cytosine arabinoside</td>
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<td>Docetaxel</td>
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<td>Interleukin-2</td>
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<td>Irinotecan</td>
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<td>Melphalan</td>
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<td>Mitomycin C</td>
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<td>Paclitaxel</td>
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<td>Procarbazine</td>
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<td>Vinorelbine</td>
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<tr>
<td><strong>Antiarrhythmic</strong></td>
<td><strong>Other</strong></td>
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<tr>
<td>Amiodarone</td>
<td>Bacille Calmette-Guérin (BCG)</td>
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<td>Tocainide</td>
<td>Mineral oil</td>
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<td>Radiation</td>
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<td><strong>Anti-inflammatory</strong></td>
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<td>Azathioprine</td>
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<td>Etanercept</td>
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<td>Gold salts</td>
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<td>Infliximab</td>
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<td>Methotrexate</td>
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<td>NSAIDs</td>
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<td>Penicillamine</td>
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<td>Sulfasalazine</td>
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<td><strong>Neurologic/Psychiatric</strong></td>
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<td>Carbamazepine</td>
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<td>Phenytoin</td>
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<td><strong>Drugs of Abuse</strong></td>
<td><strong>Chemotherapeutic</strong></td>
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<td>Cocaine</td>
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PHYSICAL EXAMINATION

- Crepitation – present in PF, frequently absent in sarcoidosis.
- Inspiratory squeaks – COP.
- Clubbing – IPF, DIP, IBD.
- Skin involvement – Sarcoidosis, CTD, Vasculitis, Tuberous sclerosis.
- Arthritis – CTD, sarcoidosis.
- Eye changes (uveitis, conjunctivitis) – Sarcoidosis, CTD.
- Muscle weakness – Polymyositis, dermatomyositis.
- Neuropathy – Sarcoidosis, CTD.
- Lymphadenopathy – Sarcoidosis, CTD.
Abnormal chest radiograph is often the first indication of underlying ILD.

Normal: Sarcoidosis, CTD, RB-ILD
### Distribution of ILD

<table>
<thead>
<tr>
<th>Upper lung zone</th>
<th>Lower lung zone</th>
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<tbody>
<tr>
<td>Sarcoidosis</td>
<td>Usual interstitial pneumonia (UIP/IPF)</td>
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<tr>
<td>Silicosis</td>
<td>Nonspecific interstitial pneumonia (NSIP)</td>
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<tr>
<td>Coal worker’s pneumoconiosis</td>
<td>Connective tissue disease–associated ILD</td>
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<tr>
<td>Hypersensitivity pneumonitis</td>
<td>Asbestosis</td>
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<tr>
<td>Langerhans cell histiocytosis</td>
<td>Desquamative interstitial pneumonia (DIP)</td>
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<td>Berylliosis</td>
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<tr>
<td>Chronic eosinophilic pneumonia</td>
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<tr>
<td>Peripheral reticular</td>
<td>Ground glass</td>
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<td>---------------------------------------------------------</td>
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<tr>
<td>Idiopathic pulmonary fibrosis/usual interstitial pneumonia</td>
<td>NSIP</td>
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<tr>
<td>Nonspecific interstitial pneumonia</td>
<td>Cryptogenic organizing pneumonia</td>
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<tr>
<td></td>
<td>Eosinophilic pneumonia (chronic or acute)</td>
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<td></td>
<td>Pulmonary edema</td>
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<td></td>
<td>Infection (opportunistic or viral)</td>
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<td>Alveolar hemorrhage</td>
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<td></td>
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<td></td>
<td>Desquamative interstitial pneumonia</td>
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<tr>
<td></td>
<td>Sarcoidosis</td>
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<td></td>
<td>Pulmonary alveolar proteinosis</td>
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<td>Nodular</td>
<td>Cystic</td>
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<td>Sarcoidosis</td>
<td>Lymphangioleiomyomatosis</td>
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<td>Berylliosis</td>
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<td>Hypersensitivity pneumonitis</td>
<td>Lymphocytic interstitial pneumonia</td>
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<tr>
<td>Langerhans cell histiocytosis</td>
<td><em>Pneumocystis jiroveci</em> pneumonia (PJP)</td>
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<tr>
<td>Silicosis</td>
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<tr>
<td>Metastatic disease</td>
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<tr>
<td>Talcosis</td>
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<tr>
<td>Granulomatous polyangiitis</td>
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<tr>
<td>(formerly known as Wegener’s granulomatosis)</td>
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<tr>
<td>Respiratory bronchiolitis ILD</td>
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</table>
• more sensitive than chest radiograph

• Radiographic Characteristics of the UIP Pattern
  • “Definite UIP”
    • Peripheral, subpleural distribution
    • Basilar predominance
    • Reticular markings and traction bronchiectasis
    • Honeycombing
    • Absence of inconsistent features
Idiopathic pulmonary fibrosis

- peripheral reticular markings
- small subpleural cysts/honeycombing
Nonspecific interstitial pneumonia

- ground-glass opacities in a peripheral distribution
- reticular markings
- Subpleural sparing is evident
- ground-glass opacities and areas of consolidation
- A 58-year-old woman with organizing pneumonia (OP) secondary to radiation for breast cancer
- Elevated angiotensin converting enzyme, hypercalcemia - Sarcoidosis
- Renal insufficiency - Pulmonary renal syndromes
- Peripheral eosinophilia - chronic eosinophilic pneumonia, EGPA, drug reaction.
Serologic testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Disease</th>
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<tbody>
<tr>
<td>ANA</td>
<td>Scleroderma, SLE, MCTD</td>
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<tr>
<td>SSA</td>
<td>Sjögren syndrome, Polymyositis</td>
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<tr>
<td>SSB</td>
<td>Sjögren syndrome</td>
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<tr>
<td>CK, Aldolase, Jo-1, Myositis-associated antibodies</td>
<td>Polymyositis, dermatomyositis</td>
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<tr>
<td>Jo-1, Myositis-associated antibodies</td>
<td>Antisynthetase syndrome</td>
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<tr>
<td>Scl-70, Anticentromere antibody</td>
<td>Scleroderma</td>
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<tr>
<td>RF, CCP</td>
<td>Rheumatoid arthritis</td>
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<tr>
<td>RNP, Antihistone antibody, p-ANCA, c-ANCA</td>
<td>Mixed connective tissue disease</td>
</tr>
</tbody>
</table>

*ANA, antinuclear antibody; CK, creatine kinase; ESR, erythrocyte sedimentation rate; SSA, anti-Ro antibody; SSB, anti-La antibody; RF, rheumatoid factor; CCP, cyclic citrullinated peptide; RNP, ribonucleoprotein; CRP, C-reactive protein; ANCA, antineutrophil cytoplasmic antibody.*
Most forms of ILD demonstrates a restrictive ventilatory defect due to decreased compliance and increased recoil of the lung parenchyma.

Presence of obstruction suggests either concomitant obstructive lung disease, or the presence of an airway-centered lung ILD such as LCH, LAM or sarcoidosis.
• useful in the diagnosis of DPLD.
• inspection of the upper and lower airways, bronchoalveolar lavage (BAL), and the performance of transbronchial lung biopsy (TBLB)
• BAL:
  • Cell count and differential,
  • Cytology,
  • Viral assays
  • Microbiologic cultures
• bloody lavage specimens - diffuse alveolar hemorrhage
• milky white BAL fluid - pulmonary alveolar proteinosis
• BAL eosinophilia (>25%) - acute eosinophilic pneumonia
• BAL lymphocytosis - granulomatous ILD, suggestive of hypersensitivity pneumonitis, drug reaction, or cellular NSIP
• Positive lymphocyte proliferation assay in chronic beryllium disease.
• Asbestos bodies in asbestosis.
• CD1a positive cells on flow cytometry may lead to a diagnosis of LCH.
• In the immunocompromised host, BAL fluid is highly sensitive for the diagnosis of bacterial, viral, fungal, and mycobacterial diseases.
• Despite a high yield in certain forms of lung disease, the utility of transbronchial biopsy for most of the IIP (such as IPF, NSIP, and LIP) is low.

• In the past surgical biopsy was often required for accurate diagnosis.

• The usual technique is video-assisted thoracoscopic surgery (VATS) that has a low morbidity and mortality in selected populations.

• However given the disease specific patterns seen on HRCT, surgical biopsy is usually not necessary at present.
TREATMENT

- REMOVAL FROM EXPOSURES
- IMMUNOSUPPRESSIVE THERAPY
- ANTIFIBROTIC DRUGS
- TREATMENT OF COMORBIDITIES
- LUNG TRANSPLANTATION
Treatment objectives in ILD

- Provide symptom-relief
- Slow down disease progression
- Prevent complications
- Improve quality of life
- Prolong survival
- Prevent treatment-complications
- End-of-Life care and palliative treatment
• Some forms of ILD, including COP, CTD–associated ILD, and sarcoidosis, shows favorable response to steroids and other immunosuppressive agents.
• When a more prolonged course of therapy is anticipated, azathioprine, mycophenolate and cyclophosphamide permit lowering the dose of steroids.
• If no clinical improvement is seen after 6 to 12 months of therapy, consider adding or changing to anti-fibrotic therapy.
Antifibrotic Agents

Pirfenidone- an oral small molecule indicated for the treatment of IPF targets p38 gamma kinase inhibitor that blocks the synthesis of TGF beta dosing titrate over 2 weeks to maintenance dose of 801 mg TID

Nitedanib-an oral small molecule indicated for the treatment of IPF, ILD with a progressive phenotype and SSc-ILD a tyrosine kinase inhibitor targeting PDGFR a/b, FGFR1-3 and VEGFR-13 dosing of 150mg every 12 hours
Pirfenidone: RELIEF Trial

Multicenter, DB, randomized, PC, parallel 2b trial

Ages 18-80 years with progressive fibrotic ILD due to CTD, NSIP, chronic hypersensitivity pneumonitis or asbestosis induced lung fibrosis

Inclusion criteria included FVC of 40-90% predicted, DLCO of 10-90% predicted and an annual decline of FVC of at least 5% predicted despite conventional therapy

Patients randomized 1:1 to placebo plus background therapy or pirfenidone added to background therapy

Length of study 48 weeks

Primary endpoint was absolute change in percentage of predicted FVC from baseline to 48 weeks in ITT population
After 127 patients had been randomized, the study was prematurely terminated on the basis of an interim analysis for futility triggered by slow recruitment.

After 48 weeks and in the overall population, rank ANCOVA with diagnostic group included as a factor showed a significantly lower decline in FVC% predicted in the treatment compared to the placebo group (p=0.042).

A significant treatment effect was also observed when applying LOCF and multiple imputation methods.

One death occurred in the treatment group (non-respiratory) and 5 deaths occurred in the control group (3 were respiratory).

The most frequent serious adverse events were infections (five in the treatment group and ten in the placebo group).

General disorders including disease worsening (2 in the treatment group and 7 in the placebo group).

Cardiac disorders occurred in one of the treatment and 5 in the placebo group.

Adverse events of nausea, SOB and diarrhea also occurred in one or two patients.
Nintedanib: SCENCIS Trial

Onset of first non-Raynaud’s symptom within past 7 years
HRCT of the lungs with fibrosis of at least 10% of the lungs
Randomized 1:1 to nintedanib or placebo
Primary endpoint was annual rate of decline in FVC assessed over 52 weeks
Secondary endpoints were absolute changes in mRSS and in the total score of the St. George’s Respiratory Questionnaire (SGRQ) at week 52
A total of 576 patients were randomized
51.9% had diffuse cutaneous systemic sclerosis
48.4% were receiving mycophenolate at baseline
In the primary endpoint analysis, the adjusted annual rate of change in the FVC was -52.4 ml per year in the treatment group and -93.3 ml per year in the placebo group (95% CI 2.9-79.0; P=0.04).

The change in baseline in the mRSS and the total score on the SGRQ did not differ significantly between the 2 groups.

Diarrhea, the most common adverse event occurred in 75.7% of the patients in the treatment group and 31.6% in the placebo group.
• Lung transplant
  • Most patients with ILD referred for lung transplantation have IPF-advanced stage.
  • a severely impaired DLCO (<39%) as well as advanced fibrosis on HRCT predict poor survival and are considered to be triggers for active listing on the transplant list.
  • Early referral to a lung transplant center is useful to plan for the future
Summary

Pulmonary complications are common in rheumatic diseases. Identification of pulmonary involvement early on in the disease course is imperative for a better long term prognosis. HRCT of the lung aids in the early detection of lung involvement, prevents the need for lung biopsy and is specific for the type of pulmonary disease present. Therapies vary depending on the type of lung involvement. More effective therapies are needed for the treatment of ILD seen in our rheumatology patients.