# Interstitial and infiltrative lung disease

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# Interstitial and infiltrative lung diseases

1. Diffuse parenchymal lung disease
   - idiopathic interstitial pneumonias
   - Sarcoidosis
2. Lung diseases due to systemic inflammatory disease
   - ARDS
   - respiratory involvement in CTD
3. Pulmonary Eosinophilia and vasculitides
4. Lung diseases due to drugs and irradiation.
5. Rare interstitial lung disease.

# Diffuse parenchymal lung disease

- A heterogeneous group of conditions
- Affecting the pulmonary parenchyma and/or alveolar lumen
- Share a common physiological and radiological similarities.

# Interstitial lung disease characterized by:

1. Clinically by respiratory symptoms and signs.
2. Radiologically diffused infiltrates.
3. Histologically by distortion of the gas exchanging units.
4. Physiologically by restriction of lung volumes and impaired oxygenation.

# WHAT DOES "INTERSTITIAL' MEAN?

- It implies specifically to the area between the alveolar epithelial and capillary endothelial basement membranes.

- This group of pulmonary disorders frequently involves:
  1. alveolar epithelium
  2. alveolar space
  3. pulmonary microvasculature
  4. respiratory bronchioles
  5. larger airways
  6. pleura

# Pathophysiology

- Primarily a disease of the interstitium

- **Repeated exposure to inflammatory agents or imperfect repair of damaged tissue leads to permanent damage.**
  - Increased interstitial tissue replaces normal structures
  - Continuing injury or imperfect repair results in progressive damage and worsening impairment.

- Physiological impairment due to damage
  - V/Q mismatch, shunt, ↓DLCO
  - These all lead to exercise intolerance.

# Classification of DPLD

- 1. DPLD of known cause : drugs, CTD
- 2. Idiopathic interstitial pneumonia:
  a) Idiopathic pulmonary fibrosis
  b) other than IPF ( desquamative, AIP, NSIP, COP, LIP, respiratory bronchiolitis)
- 3. Granolomatous DPLD : sarcoidosis
- 4. Others: Histiocytosis X.

# Clinical work up

1. Patient's history

2. physical examination

   - general

   - systemic

## Work up by appropriate investigations

1. Laboratory investigations
2. Radiograph ( x-ray, HRCT)
3. Pulmonary function test
4. Brochoalveolar lavage
5. Biopsy ( Transbronchial, surgical, cryobiopsy)

# MODES OF CLINICAL PRESENTATION

1. -Cough, which is typically dry and distressing, -Breathlessness, which is often insidious in onset and relentlessly progressive.
2. Respiratory symptoms associated with another disease such as a connective tissue disease.
3. No respiratory symptoms but abnormal chest radiograph. [Normal chest radiograph does not R/O ILD.]
4. Abnormal PFT, especially restrictive ventilatory pattern.

# HISTORY

1. Age
2. Gender
3. Smoking
4. Duration
5. Intensity
6. Occupational
7. Drugs
8. Specific exposure
9. Comorbidities

## PHYSICAL EXAMINATION

- "End inspiratory crepitations" are common in most forms of ILD.
  - These are less likely in sarcoidosis.
- Clubbing: most commonly seen in IPF but non-specific.
  - Rare in EG, Sarcoidosis, HP.
- Corpulmonale.
- Cynosis in late stage of ILD.
- Extrathoracic findings: directive but not diagnostic.

# Laboratory investigations

- FBC:

  - Lymphopenia in sarcoid

  -Eosinophilia in pulmonary eosinophilia and drugs.

- ESR and CRP
- Ca+, ACE in sarcoid.
- Autoimmune screening :

  ANCA/Anti-GBM

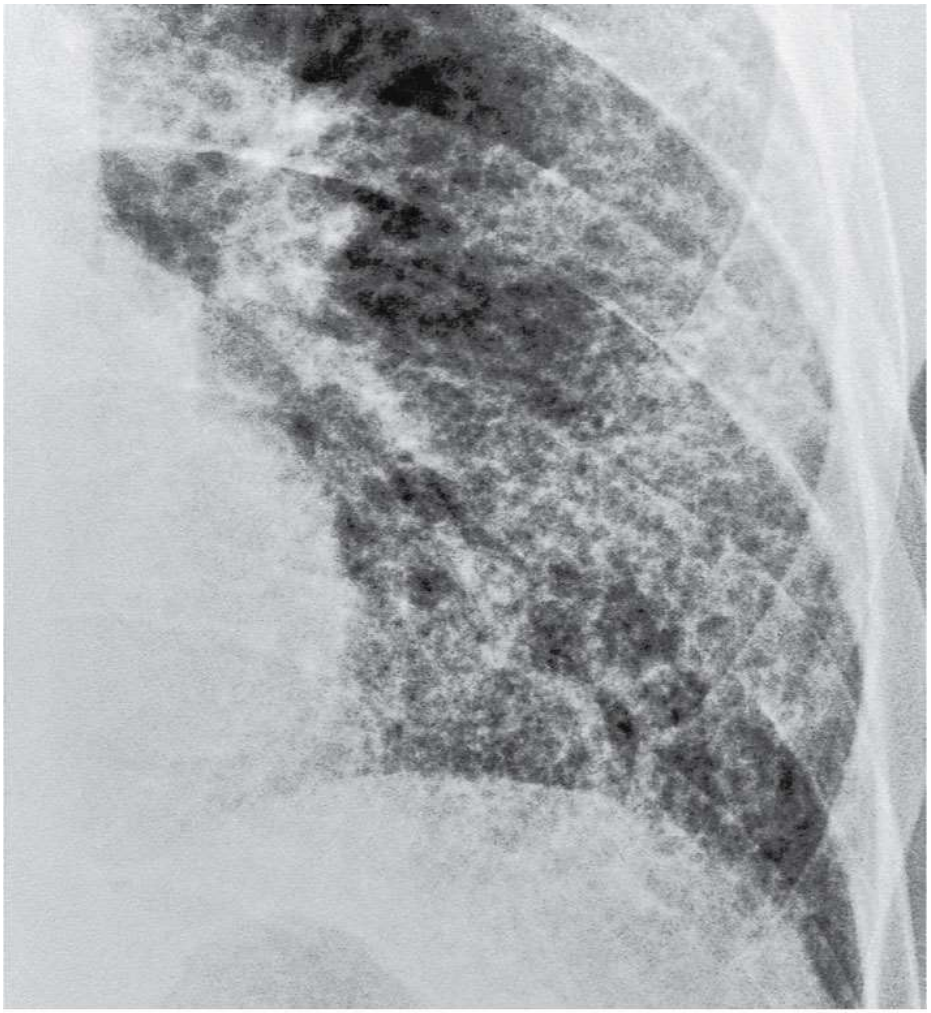
  RF/ANA/Anti-DNA

# CHEST RADIOGRAPH

- ILD is often suspected on the basis of an abnormal chest x-ray.
- Review all previous films to assess the rate of change in disease activity.
- Remember, chest radiograph is normal in 10% of patients with ILD (particularly those with HP).

# Common radiologic findings:

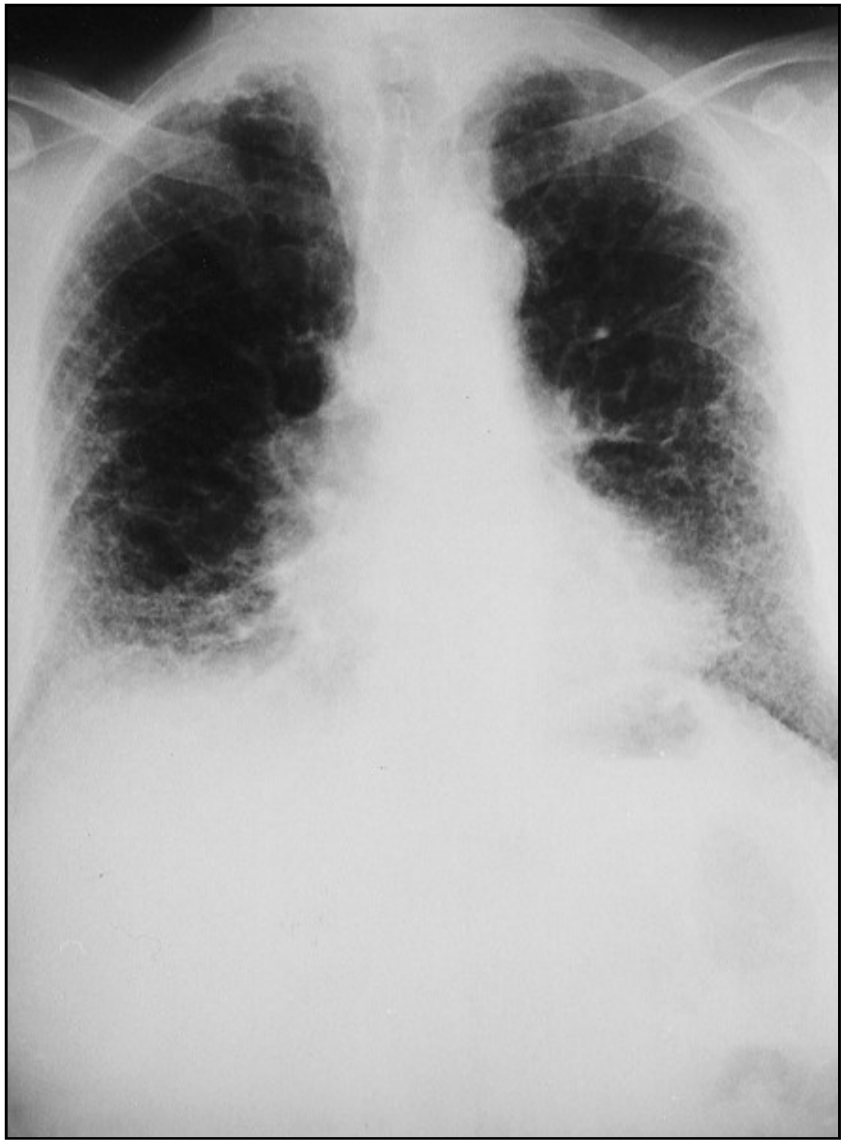
- -bilateral reticulonodular pattern
- Irregularly shaped opacities
- Granulomas
- Cavity formation
- Honeycombing
- Pleural effusion



(From Hansell DM, Armstrong P, Lynch DA, McAdams HP, eds: *Imaging of diseases of the chest,* ed 4, Philadelphia, 2005, Elsevier.)

Fig. 25-2. Reticulonodular pattern of interstitial pulmonary fibrosis in a patient with scleroderma.

**Reticulonodular pattern of interstitial pulmonary fibrosis in a patient with scleroderma.**



**Chest x-ray film of a patient with asbestosis.**

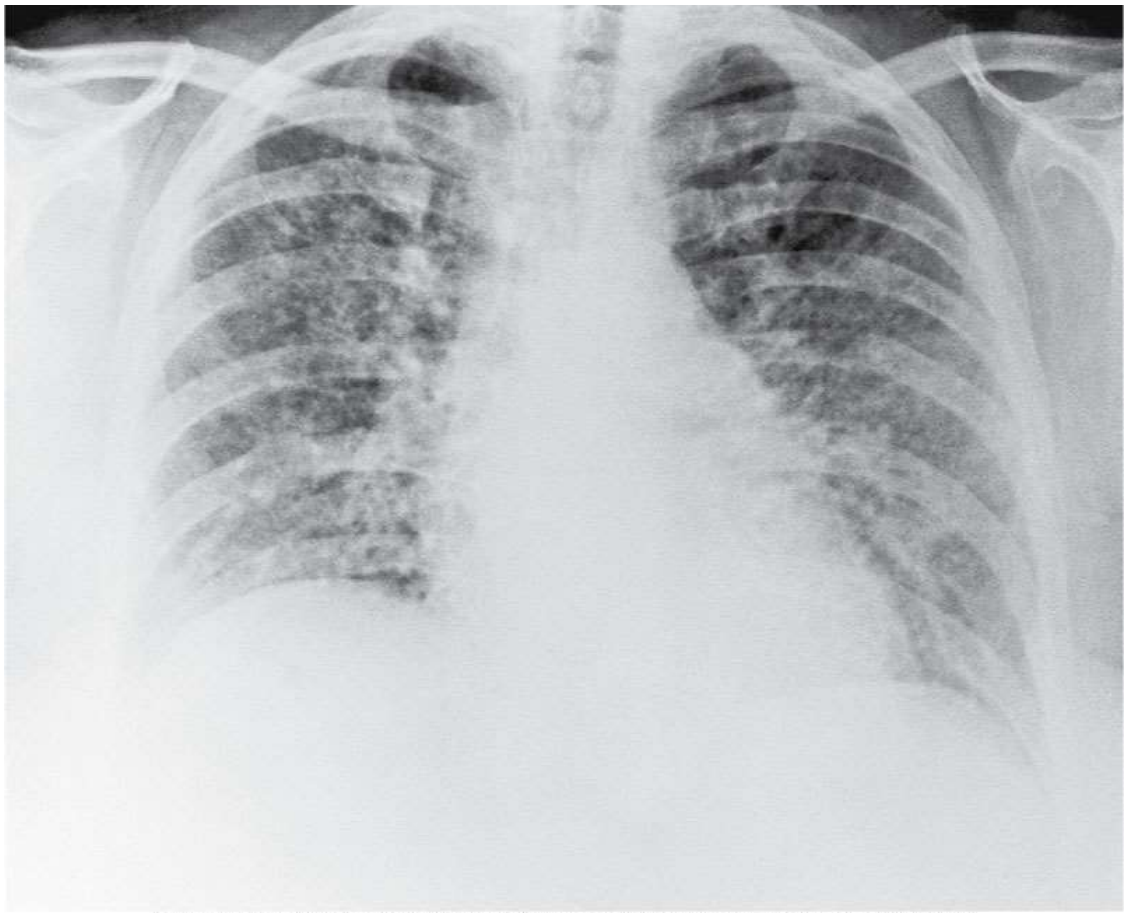


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Fig. 25-5. Acute farmer's lung. Chest radiograph shows diffuse parenchymal ground-glass pattern with some areas of consolidation. The severity of parenchymal opacification in this case is unusual.

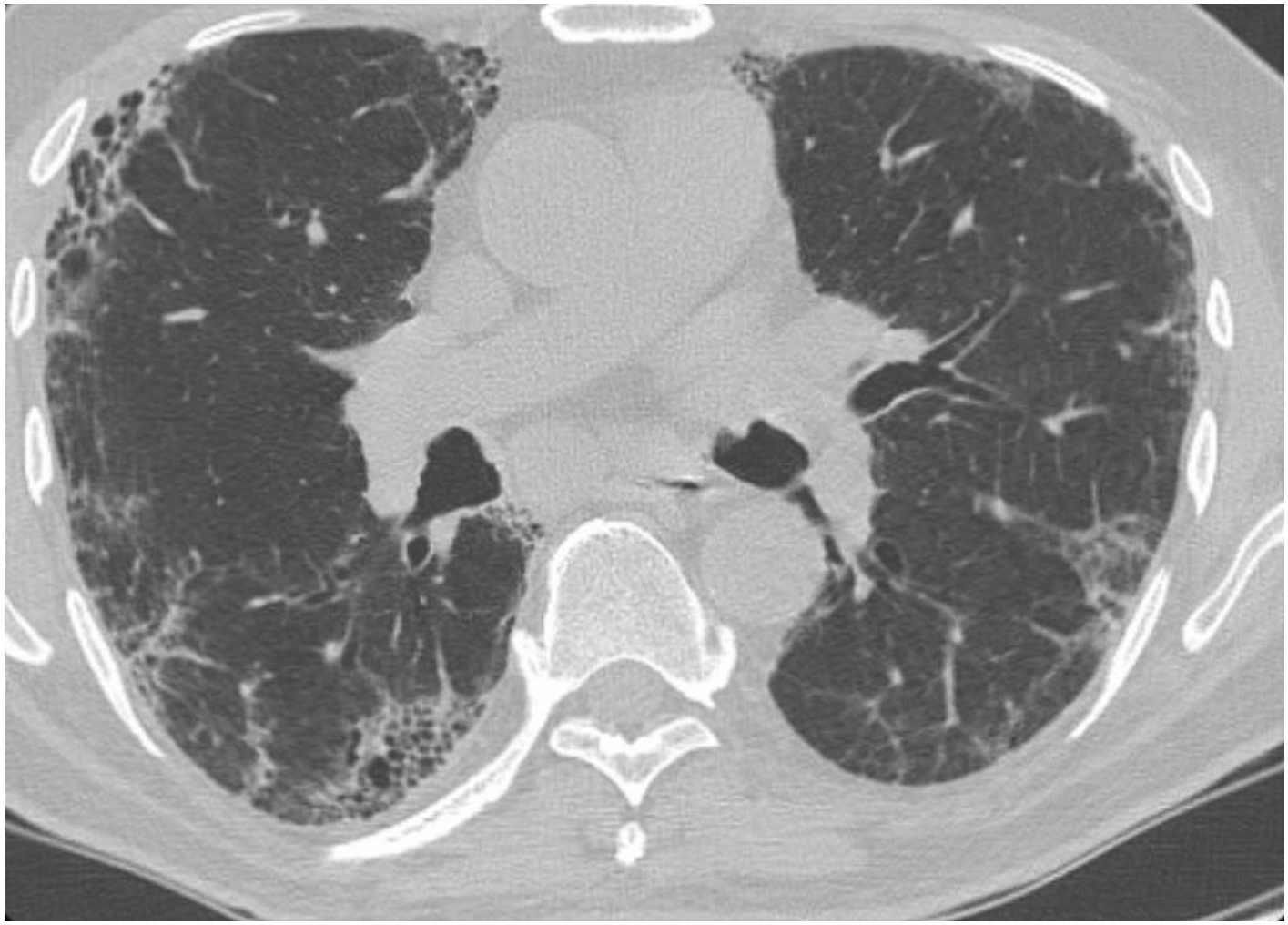
**Acute farmer's lung. Chest radiograph shows diffuse parenchymal ground-glass pattern with some areas of consolidation. The severity of parenchymal opacification in this case is unusual.**

# HRCT Scan

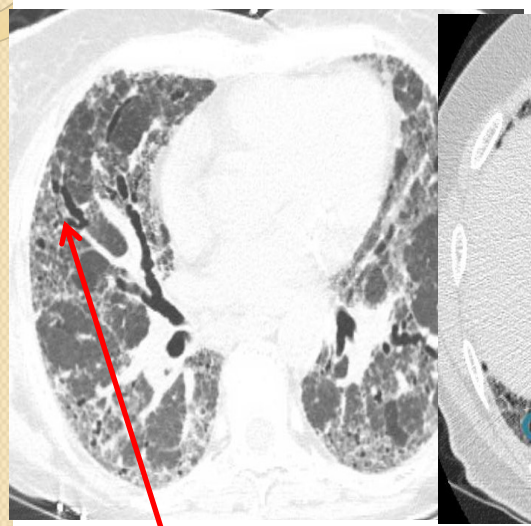
1. Ground glass opacities
2. Reticulo nodular shadow
3. Honeycombing
4. Traction bronchiectasis

Presence of Honeycombing

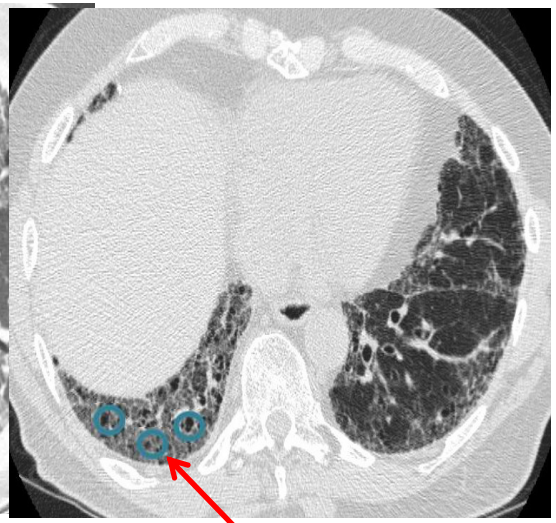
- Key characteristic of UIP pattern
- Defined as clustered, thick-walled cystic spaces of similar diameters
- Typically located in dorsal, basal, and subpleural regions
- Sometimes seen only in upper lungs
- Honeycombing increases likelihood of UIP pattern



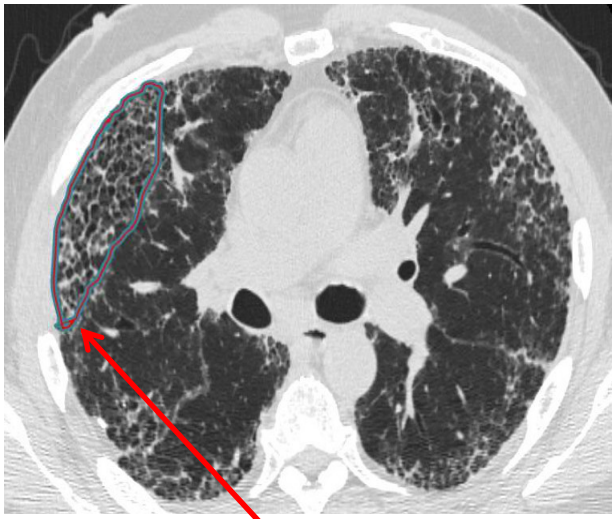
# CT Changes With IPF (images)



Traction bronchiectasis



Traction bronchiolectasis



Honeycombing

# Pulmonary function test

- Most patients with IPF exhibit the following:
  - Decreased FVC (FVC may be normal in early IPF)
  - Normal-to-increased $FEV_1$/FVC ratio
  - Reduced DLCO
  - Reduction in TLC
- Low baseline FVC, decline in FVC, low DLCO, and decline in 6MWT are associated with decreased survival

# Lung biopsy

- 1. Surgical lung biopsy
- 2. Cryobiopsy
- 3. Transbronchial biopsy

## Cryobiopsy

Cryoprobe cooled to -85° to -95°C is applied to desired tissue

Cryobiopsy samples much smaller than surgical lung biopsy samples

Results in ~80% correct diagnosis

Diagnostic yield and complication rate are variable and depend on operator's experience

# BRONCHOALVEOLAR LAVAGE

- It is often the initial procedure of choice

- BAL: normal count:
  - CD4:CD8 = 1.5
  - Macrophage 85% , Lymphocyte 5-10%
  - Neutrophils $\leq$ 2%, Eosinophils $\leq$ 1%.

- CD4:CD8: > 2 is seen in sarcoidosis, TB, fungal infection.

- CD4: CD8 < 1 is seen in hypersensitivity pneumonitis.

# Current Treatment Options

1. Supportive care and nonpharmacologic measures
2. Medical management
3. Treatment of exacerbations (unproven)
4. Lung transplant (only in select patients with advanced IPF)

# 1. Supportive Management of ILD

- Oxygen Therapy Protocol
  - Recommended when patient's desaturation is < 88% during 6MWT
  - Nocturnal oxygen with sleep apnea

- Bronchopulmonary Hygiene Therapy Protocol
  - Aerobic conditioning
  - Education about condition
  - Nutritional counseling
  - Psychosocial support

- Mechanical ventilation
- Palliative care services

# 2. Therapeutic Strategies for IPF

- **Nintedanib**: Tyrosine kinase inhibitor
  - Reduces fibrogenesis
  - Prolonged time to acute exacerbation
  - Reduced rates of FVC decline

- **Pirfenidone:** Distinct antifibrotic properties
  - Reduced disease progression
  - Reduced rates of FVC decline
  - Improved progression-free survival
- Check liver function before initiating therapy, also during treatment

# Other treatments

- PPI to control gastro esophageal reflux.
- Smoking cessation
- Vaccination ( Influenza and pneumococcal)
- Avoidance of exposure/ environment
- Domiciliary oxygen and pulmonary rehabilitation
- If exacerbations, broad spectrum antibiotics and glucocorticoids.

# Treatment of other form of DPLD

- According to causes.

-Example:

Sarcoidosis

– corticosteroids.

Tropical pulmonary Eosinophilia

- diethylcarbamazine.

# Disease Monitoring

- Continue pulmonary function tests (PFT)
- 6MWT used for prognostication
- Assess treatment response

# Latest Research on Emerging Therapies

| Compound | Company | Structure/Route of Administration | Stage of Development | Mechanism of Action | Background Therapy | ClinicalTrials.gov Identifier: |
|---|---|---|---|---|---|---|
| PRM-151 | Promedior/ BMS | mAb/IV | Phase 2 | Rh-pentraxin-2 protein | pirfenidone or nintedanib allowed | NCT02550873 |
| SAR-156597 | Sanofi | mAb/SC | Phase 2 | Anti IL-4/IL-13 | pirfenidone or nintedanib allowed | NCT02345070 |
| FG-3019 | Fibrogen | mAb/IV | Phase 2 | Anti-CTGF | pirfenidone or nintedanib allowed only in the sub study | NCT01890265 |
| STX-100/BG00011 | Biogen | nAb/SC | Phase 2 | Anti-integrin avB6 | pirfenidone allowed | NCT01371305 |
| PBI-4050 | Prometric | Sm/oral | Phase 2 | CTGF expression inhibitor | pirfenidone or nintedanib allowed | NCT02538536 |
| TD139 | Galecto/B | Sm/Inhalation | Phase 2 | Galectin-3 | Not allowed | NCT02257177 |

Sm, small molecule; mAb, monoclonal antibody; IV, intravenous; SC, subcutaneous; IL, interleukin; CTGF, connective tissue growth factor; BMS, Bristol-Meyers Squibb.

# Latest Research on Emerging Therapies *(cont)*

| Compound | Company | Structure/Route of Administration | Stage of Development | Mechanism of Action | Background Therapy | ClinicalTrials.gov Identifier: |
|---|---|---|---|---|---|---|
| MN-001 (tipelukast) | MediciNova | Sm/oral | Phase 2 | Leukotriene receptor antagonist | nintedanib allowed | NCT02503657 |
| KD025 | Kadmon | Sm/oral | Phase 2 | ROCK2 inhibitor | Not allowed | NCT02688647 |
| CC-90001 | Calgene | Sm/oral | Phase 2 | JNK1 inhibitor | NA | NCT03142191 |
| GLPG-1690 | Galapagos | Sm/oral | Phase 2 | Autotaxin inhibitor | NA | NCT02738801 |
| Omipalisib | GSK | Sm/oral | Phase 2 | P13K/mTOR | NA | NCT10725139 |
| GBT440 | Global Blood Therapeutics | Sm/oral | Phase 2 | Hb O2 release stimulant | NA | NCT02846324 |

Sm, small molecule; mAb, monoclonal antibody; IV, intravenous; ROCK2, Rho-associated protein kinases; JNK, Jun N-terminal kinases; PI3K, Phosphoinositide 3-kinases; mTOR, mammalian target of rapamycin; GSK, GlaxoSmithKline.

ClinicalTrials.gov

# Take home message

In chronic cases, careful history, physical examination and appropriate investigations are mandatory to differentiate IPF from occupational exposure, medications or connective tissue diseases.

In acute presentation, it is important to differentiate acute interstitial pneumonia from ARDS.

An early diagnosis and appropriate management are vital to maintain quality of life and slow disease progression.

köszönöm תודה! děkuji

mahalo 고맙습니다

thank you

merci 谢谢 danke

Ευχαριστώ شكرا

どうもありがとう gracias