The recent advances made in treating ILD specially IPF

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Introduction and background

- ILD is a group of disorders that affect the Lung parenchyma which includes the alveoli, the alveolar epithelium, the capillary endothelium, and spaces between these structures.
- ILD is also known as diffuse parenchymal lung disease. This condition involves a series of inflammations and fibrosis of the lung parenchyma, disrupting the normal physiology of the respiratory system.

Introduction and background

Known Cause

- CTDs
- Environmental & Occupational
- Drugs & Radiation
- Smoking (RB-ILD/DIP, PLCH, AEP)
- Rare forms (LAM, PAP, amyloid, microlithiasis, heritable disorders, etc.)

Unknown Cause

- IPF and other IIPs (iNSIP, COP, iLIP, AIP, iPPFE)
- Sarcoidosis
- iEosinophilic pneumonias
- Vasculitis
- Rare forms (IgG4-RD, Erdheim Chester, etc.)

Introduction and background

Usual interstitial pneumonia

- **UIP is the most specific form of the IIPs**
- **The histologic hallmark and chief diagnostic criterion for UIP is a ⇨ heterogeneous appearance with alternating areas of normal lung, interstitial inflammation, fibroblast foci, and honeycomb change.**

The clinical counterpart of UIP is Idiopathic Pulmonary Fibrosis (IPF)

Clinical features

- **The most common symptom seen in patients is Dyspnea of gradual onset.**
- But sometimes they may also present with symptoms as simple as **Coughing** .
- **Pleuritic chest pain** is uncommon, but doctors can visualize such symptoms in conditions like **sarcoidosis.**
- **Diffuse alveolar hemorrhage** can lead to **Hemoptysis** in patients with ILD.

Investigations

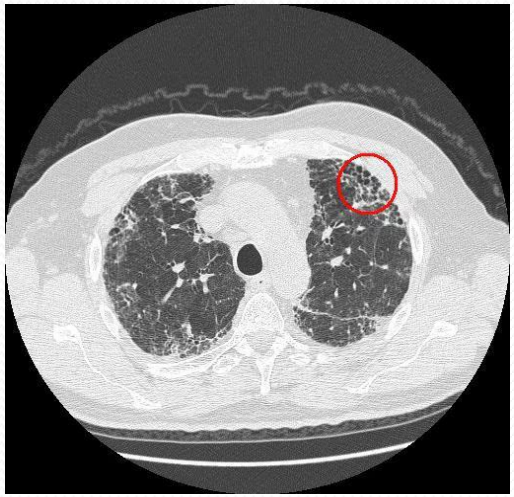
- The first radiological investigation done in ILD patients is a chest X-ray, but it is rarely sufficient
- Lung function tests include Spirometry and DLCO
- Oximetry
- Blood tests are used to diagnose autoimmune illnesses and other inflammatory reactions to environmental immunogenic responses by detecting proteins, antibodies, and other indicators.
- Echocardiogram findings may be normal.

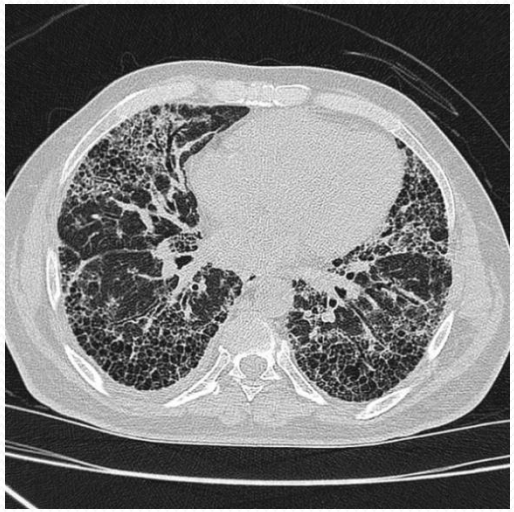
Investigations

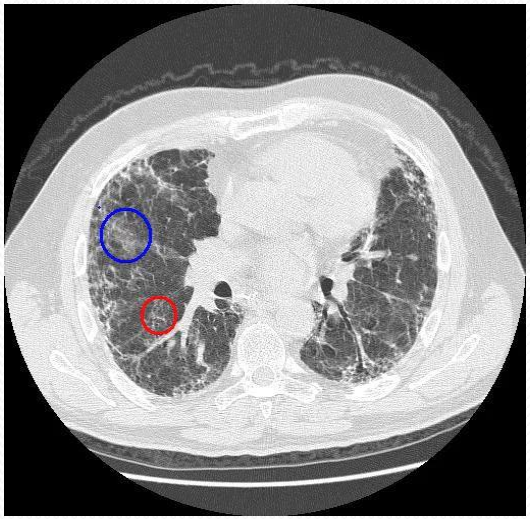
- **HRCT** is **the investigation of choice and** can help determine the extent of disease
- The characteristic HRCT features of IPF include **peripheral, basilar-predominant opacities** associated with **honeycombing** and **traction bronchiectasis-bronchiolectasis.**

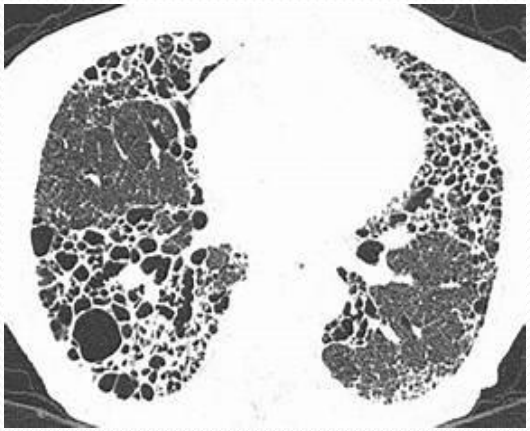
This has removed the need for invasive techniques for making the diagnosis

HRCT of IPF









Investigations

- **A surgical lung biopsy is the current gold standard for obtaining tissue samples and diagnosing unclassifiable ILD**
- **Transbronchial cryobiopsy (TBCB) is an acceptable alternative to surgical lung biopsy in centers with expertise**
- **Transbronchial lung biopsy (TBLB) is generally too small to secure a definitive histopathologic diagnosis of UIP.**
- **Bronchoalveolar lavage could be helpful.**

Pharmacological treatment

How to approach cases

- For patients with mild or moderate IPF

Initiating therapy with either:

Nintedanib or Pirfenidone

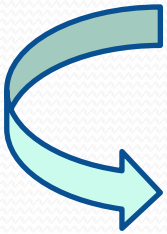
How to approach cases

- **For patients with more advanced IPF:**

FVC <50 percent predicted

DLCO <35 percent predicted

Initiating therapy with either:



Nintedanib

or

Pirfenidone

Observational studies suggest that both agents slow disease progression in patients with more advanced disease to a similar extent as that seen in treated patients with less advanced disease

23. Harari S, Caminati A, Poletti V, et al. A Real-Life Multicenter National Study on Nintedanib in Severe Idiopathic Pulmonary Fibrosis. Respiration 2018; 95:433.

How to approach cases

- **Patients with severe pulmonary hypertension**

(systolic pulmonary artery pressure ≥60 mmHg) due to advanced IPF

--Inhaled Treprostinil

--Systemic Prostanoids

--Sildenafil

may be beneficial in this population.

Nintedanib

A receptor blocker for multiple Tyrosine Kinases that mediate elaboration of Fibrogenic growth factors

--Vascular endothelial growth factor(VEGFR)

--Platelet-derived growth factor

--Fibroblast growth factors

Slows the rate of disease progression in IPF

Nintedanib in progressive fibrosing interstitial lung diseases. Flaherty KR, Wells AU, Cottin V, et al. *N Engl J Med.* 2019;381:1718–1727.

Nintedanib

- **In addition to blocking tyrosine kinase receptors, it also helps in blocking non-tyrosine kinase receptors, i.e., Src and Lck, directly, thus :**

  ⇒ **Preventing fibroblast activation**

  ⇒ **Inhibiting fibroblast proliferation and migration**

Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. Wollin L, Wex E, Pautsch A, Schnapp G, Hostettler KE, Stowasser S, Kolb M. *Eur Respir J.* 2015;45:1434–1445. [

Nintedanib

Efficacy

In clinical trials, the main benefits of Nintedanib are:

= A reduction in the rate of decline in lung function

(the rate of decline in (FVC) among untreated patients is 150 to 200 mL per year)

= A longer time to first exacerbation

Richeldi L, Cottin V, du Bois RM, et al. Nintedanib in patients with idiopathic pulmonary fibrosis: Combined evidence from the **TOMORROW** and **INPULSIS**(®) trials. Respir Med 2016; 113:74

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Richeldi L, Kreuter M, Selman M, et al. Long-term treatment of patients with idiopathic pulmonary fibrosis with nintedanib: results from the **TOMORROW** trial and its open-label extension. Thorax 2018; 73:581.

Dosage

- **The recommended dose is 150 mg twice daily, to be taken whole with food.**
- **Liver function tests; [ALT], [AST], bilirubin should be assessed prior to initiation of Nintedanib**
- **In case of any side effects, a reduction in the drug dose is advised to 100mg twice a day**
- **A pregnancy test should be performed prior to initiation of therapy in women of child-bearing age, and conception avoided until at least three months after the last dose**

Nintedanib. US Food and Drug Administration (FDA) approved product information. US National Librar y of Medicine. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=da1c9f37-779e-4682-816f-93 dofaa4cfc9 (Accessed on November 10, 2014).

Dosage

- When administering nintedanib, other precautions must be taken for drugs that are metabolized by CYP3A4 and P-glycoprotein enzymes, as this alters the bioavailability and metabolic activity of these drugs.
- Drugs like Omeprazole, Barbiturates, Phenytoin, Amoxicillin, Azithromycin, Ketoconazole, and Rrifampicin can affect its metabolism.

Adverse effects

- **Diarrhea** (diarrhea led to permanent dose reduction in 11 percent of patients)
- **Nausea, vomiting,, pain in the abdomen**
- **Decrease in appetite**
- **Elevation of liver enzymes**
- **Coughs, respiratory tract infections,**
- **Urinary tract infections,**
- **Skin rashes, and ulcers are seen.**

Contraindications

- **Nintedanib usage is not recommended in conditions of pregnancy and lactation.**
- **A highly effective contraceptive is advised for females who are in their reproductive age group, which should be started before medication.**

Contraindications

- The continuation of contraceptives must be done for at least three months after the last dose of Nintedanib.
- Breastfeeding during this Nintedanib therapy is usually not advised.
- Moderate or severe liver impairment is also a contradiction in Nintedanib treatment.
- Tobacco usage decreases the effectiveness of this therapy.

Gastrointestinal adverse effects of nintedanib and the associated risk factors in patients with idiopathic pulmonary fibrosis. Kato M, Sasaki S, Nakamura T, et al. *Sci Rep.* 2019;9:12062

Pirfenidone

The predominant pathological findings in IPF are:

- **Fibroblast foci**
- **Collagen deposition**
- **Minimal inflammatory cell infiltration**

Raising the possibility that antifibrotic agents might slow the rate of disease progression .

2. Scotton CJ, Chambers RC. Molecular targets in pulmonary fibrosis: the myofibroblast in focus. Chest 2007; 132:1311 .

Pirfenidone

Pirfenidone is an antifibrotic agent that

1- Inhibits transforming growth factor beta (TGF-b) -stimulated collagen synthesis

2- Blocks fibroblast proliferation in vitro

3- By inhibiting TGF-beta 1, it also inhibits the conversion of fibroblasts in the human lung into myofibroblasts,

Safety, tolerability, and efficacy of pirfenidone in patients with rheumatoid arthritis-associated interstitial lung disease: a randomized, double-blind, placebo-controlled, phase 2 study. Solomon JJ, Danoff SK, Woodhead FA, et al.

Pirfenidone

- The efficacy of pirfenidone against IPF has been demonstrated in several randomized controlled placebo trials and over one decade of real-world experiences.
- **Pirfenidone** ⇨

  -- Mitigate the decline in lung function

  -- Reduce the risk of death

  -- Lengthen progression-free survival

King TE, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis.New Engl J Med. (2014) 370:2083–92.

Pirfenidone

(ASCEND) trial

- In the ASsessment of pirfenidone to Confirm Efficacy aND safety in idiopathic pulmonary fibrosis (ASCEND) trial, **555 patients with IPF were randomly assigned to receive oral pirfenidone (2403 mg per day) or placebo for 52 weeks** [58]. Pirfenidone resulted in a significant reduction in the one-year rate of decline in FVC; the proportion of patients in the pirfenidone group who had a decline of 10 percentage points or more in the percent of predicted FVC or died was reduced by 48 percent compared with the placebo group (46 patients [16.5 percent] versus 88 patients [31.8 percent]), respectively. Nearly 23 percent of the pirfenidone group had no decline in percent of predicted FVC at week 52, compared with 10 percent of the placebo group, representing a more than 133 percent increase in the proportion of patients with no evidence of FVC decline. As secondary end-points, **pirfenidone reduced the rate of decline in the six-minute walk difference and improved progression-free survival compared with placebo** but **did not reduce dyspnea**. In a prespecified analysis that pooled results of the ASCEND trial with two prior trials (CAPACITY 004 and 006; 1247 total patients) [53], pirfenidone **decreased death from any cause relative to placebo** (22 [3.5 percent] in the pirfenidone group as compared with 42 [6.7 percent] in the placebo group; HR 0.52, 95% CI 0.31-0.87). As the ASCEND trial was 52 weeks in duration, the pooled survival analysis only considered data from the first 52 weeks of the CAPACITY ● trials (which were 72 weeks in duration). A separate pooled analysis considering all available data on all-cause mortality showed a trend favoring pirfenidone but was not statistically significant (KaplanMeier estimate 0.75, 95% CI 0.51-1.11)

. King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014; 370:2083

Pirfenidone

CAPACITY 004 and 006)

- Two concurrent, multicenter trials (Clinical studies Assessing Pirfenidone in idiopathic pulmonary fibrosis, CAPACITY 004 and 006) **assessed the change in percentage FVC at week 72** [53]. Patients with mild-to-moderate IPF (ie, FVC ≥50 percent predicted and DLCO ≥35 percent predicted) were randomly assigned to oral pirfenidone **2403 mg/day**, **1197 mg/day**, or placebo in the 004 trial and oral pirfenidone 2403 mg/day or placebo in the 006 trial. **The higher dose of pirfenidone significantly decreased the percent fall in FVC in the 004 trial** (difference between groups 4.4 percent, p = 0.001) **but not the 006 trial** (difference between groups 0.6 percent, p = 0.51). The **higher dose of pirfenidone** significantly **reduced the decline in the six-minute walk test,** a secondary endpoint, in the 006 (absolute difference 32 meters, p = 0.0009), **but not the 004 trial.**

53. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet 2011; 377:1760.

Pirfenidone

separate multicenter trial

- In a separate multicenter trial, 275 patients were randomly assigned to one of three groups: **pirfenidone 1800 mg per day, 1200 mg per day,** or placebo. The primary endpoint, change in VC, was assessed at **52 weeks**; the secondary endpoint was progression-free survival. **The decline in VC was only slightly less in the high-dose pirfenidone group** compared with placebo, but the difference was statistically significant. **The progression-free survival time was slightly longer in the high-dose pirfenidone** group compared with placebo.

. Taniguchi H, Ebina M, Kondoh Y, et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J 2010; 35:821.

Dosage

- **Pirfenidone is initiated at a dose of :**

  ⇒ **267 mg (1 capsule) three times a day**

  (one week)

  ⇒ **534 mg (2 capsules) three times a day**

  (second week)

  ⇒ **801 mg (3 capsules) three times a day**

  Pirfenidone should always be taken with food

Adverse effects

- **Gastrointestinal disturbances, diarrhea, nausea, and vomiting.**

  (Dose reduction or interruption for gastrointestinal events was required in 18 percent of patients in the 2403 mg/day group)

- **Skin rash**

Adverse effects

- **Some less common side effects include:**
  - -- **Black stools**
  - -- **Loosening of the skin**
  - -- **Chest pain**
  - -- **Chills**
  - -- **General feeling of tiredness or weakness**
  - -- **Joint or muscle pain**

Adverse effects

- **These drugs pose no risk of teratogenicity**
- **No problems are seen during pregnancy or breastfeeding.**

Contraindications

- Patients with hepatic impairment so ((LFTs should be monitored monthly for the first six months and at three month intervals thereafter))
- Patients with CrCl <15 mL/min or patients on dialysis
- Hypersensitivity reactions to the drug

Pirfenidone. US Food and Drug Administration (FDA) revised label: https://www.accessdata.fda.gov/dru gsatfda_docs/label/2023/208780s007,022535s016lbl.pdf (Accessed on March 07, 2023).

Precautions

- **The dose of Pirfenidone should be reduced in the presence of strong or moderate CYP1A2 inhibitors (eg, fluvoxamine, ciprofloxacin)**
- **patients with CrCl <30 mL/min; need close monitoring and possible need for dose adjustment.**

Pirfenidone in idiopathic pulmonary fibrosis. Taniguchi H, Ebina M, Kondoh Y, et al. *Eur Respir J.* 2010;35:821–829.

Surgical Management

Lung transplantation:

- **This procedure extends and improves the quality of life for patients with ILD.**
- **These operations include:**
  - -- **Single lung transplant**
  - -- **Double lung transplant**
  - -- **Heart and lung transplantation**
- A single lung transplant was technically a more straightforward procedure and had less morbidity and mortality

Recent advances in lung transplantation. Meyer KC. *F1000Res.* 2018;7:1684.

Surgical Management

Transplant candidates are scored depending on medical information such as:

- **Forced vital capacity**
- **Pulmonary artery pressure**
- **Oxygen at rest**
- **Age**
- **Body mass index**
- **Six-minute walk distance**
- **Diabetes**
- **Functional status**
- **And many more…**

Surgical Management

General guidelines for timing of referral for transplantation include histologic or radiographic evidence of usual interstitial pneumonia (UIP) and the following:

- **(DLCO) <40 percent of predicted**
- **(FVC) <80 percent of predicted**
- **Any dyspnea or functional limitation attributable to lung disease**
- **A decrease in pulse oximetry below 89 percent saturation, even if only during exertion**

Surgical Management

Criteria for placing on transplant list include the following :

- **Decline in FVC ≥10 percent during six months of follow-up (a decline ≥5 percent may also warrant listing)**
- **Decline in DLCO ≥15 percent during six months of follow-up**
- **On six-minute walk test (over six months) :**

  -- Oxygen desaturation to <88 percent

  or -- Distance walked <250 meters

  or -- >50 meter decline in distance walked

Surgical Management

- Pulmonary hypertension on right heart catheterization or transthoracic echocardiogram
- Hospitalization because of respiratory decline, pneumothorax, or acute exacerbation

Surgical Management

General contraindications and difficulties:

1- The donor shortage situation

2- Reduced support from society in some coutries

3-Evidence of tuberculosis

4-Deformities with the spine and chest wall

5-Usage of abusive substances like tobacco or others

6-Mental abnormalities with impaired ability to cooperate

7- Untreatable significant organ damage

8-Any previous history of malignancy

9-Obesity with a BMI >35kg/m2.

Gender-Age-Physiology (GAP) model

- When developing a treatment plan for each patient, it is helpful to have an estimate of prognosis.
- GAP model, incorporates age, gender, FVC, and DLCO into a simple point-score index and staging system predictive of one, two, and three-year mortality.

Gender-Age-Physiology (GAP) model

The GAP index and staging system, combined with clinical impression, can be used to guide initial patient discussions regarding:

- **Prognosis**
- **Therapeutic options**
- **Urgency of lung transplantation**
- **Timeline of palliative approaches**

When to start treatment with antifibrotic drugs

Treatment with specific drugs for IPF should be started as soon as diagnosis is made for many reasons:

- **IPF is characterised by a very poor prognosis, the median survival at the time of diagnosis is 3– 5 years.**
- ***PF behaviour is unpredictable:* A good number of patients show a relatively slow course, other patients may show a rapid progression of the disease**

When to start treatment with antifibrotic drugs

- **Several retrospective and prospective studies have shown that a 10% decline in FVC within either 6 months or 12 months is associated with a significant increase in mortality .**

  ((According to ZAPPALA *et al*, a decline in % predicted FVC of 5–10% is related to a two-fold increase in the risk of mortality at 24 weeks, while a decline ≥10% is associated with a nearly five-fold increase in the risk of mortality over the subsequent year.))

When to stop therapy

- **There are two main reasons to stop a therapy:**

  -- Unbearable side-effects

  and/or

  -- Lack of efficacy

- **Clinical trials demonstrated that the side-effects are generally mild and rarely result in treatment discontinuation.**
- **In most cases, temporary reduction of the definitive dose may also allow the drug to be continued.**

When to stop therapy

- **Should the antifibrotic therapy be discontinued during an evident functional decline?**
- **A recent article by NATHAN *et al*. showed that a total of 34 patients (5.5%) in the pirfenidone group and 68 patients (10.9%) in the placebo group experienced a decline of ≥10% in FVC after 6 months.**
- **Interestingly, only a few patients (5.9%) in the pirfenidone group experienced a further decline of ≥10% in FVC during the subsequent 6 months, compared to 27.9% of patients in the placebo group, with only one death (2.9%) in the pirfenidone group *versus* 14 deaths (20.6%) in the placebo group.**

SUPPORTIVE CARE

- **The most important components include provision of supplemental oxygen (when needed),**
- **education (including advice about smoking cessation)**
- **pulmonary rehabilitation**
- **vaccination against respiratory infections.**
- **Palliative symptom relief for dyspnea or cough**
- **Affective disorders are common during the course of IPF and may need separate attention**

FUTURE DIRECTIONS

Combination nintedanib plus pirfenidone

Pamrevlumab

Pentraxin 2

Lysophosphatidic acid receptor 1 antagonists (BMS-986278)

Phosphodiesterase 4B inhibitor (BI 1015550)

Interstitial Lung Diseases Treatment

Treat identifiable cause / underlying disease, such as:

- **CTDs ⇨ immunosuppressive therapy, consider antifibrotic**
- **Drug or inhalational exposures ⇨ avoidance, ±glucocorticoids**
- **Smoking-related ILDs ⇨ smoking cessation, ±glucocorticoids**

Idiopathic Interstitial Pneumonias Treatment

When idiopathic:

- **IPF ⇨ antifibrotic therapy**
- **iNSIP ⇨ immunosuppressive therapy, consider antifibrotic**
- **COP ⇨ glucocorticoids ± other immunosuppressive**
- **AIP ⇨ supportive therapy, ± glucocorticoids**

iPPFE ⇨ supportive therapy

Supportive therapy/rehab, manage comorbidities, lung transplant

Thank You !