New Horizons... The Future of IPF and ILD

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Conflict of interest disclosure

I have the following real or perceived conflicts of interest that relate to this presentation:

- InterMune (Drug Study Steering committees)
- Actelion (Drug Study Steering Committees)
- ImmuneWorks (Scientific Advisory Committee)
- GlaxoSmithKline (Consultant)
- Boehringer Ingelheim (Consultant)
- Daiichi Sankyo (Consultant)
- NIH IPFnet (Principal investigator)
- UpToDate (Editor, Author)

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What have we tried...

- Cyclophosphamide
- Azathioprine
- Colchicine
- IFN-γ
- Warfarin
- Pirfenidone
- IFN-γ
- Sildenafil
- Ambrisentan

Anti-inflammatory
Immunomodulation
Immunosuppression
Anti-fibrotic
Anti-oxidant
Anti-proliferative

RCT IN IPF

- INPULSIS 1 & 2
- ASCEND
- PANTHER
- STEP IPFnet
- ACE-IPF
- King '11
- Noble '11
- Raghu '08
- Daniels '10
- King '09
- Demedts '05
- Azuma '05
- Johnson '89

Slide courtesy of Luca Richeldi
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FDA News Release

FDA approves Esbriet to treat idiopathic pulmonary fibrosis

FDA approves Ofev to treat idiopathic pulmonary fibrosis

The FDA granted Esbriet (pirfenidone) and Ofev (nintedanib) fast track, priority review, orphan product, and breakthrough designations.

We have have NOT found the holy grail!

There is no cure for IPF/UIP.
Who Should Be Prescribed These Drugs?

- Any age (usually >50 yrs)
- Confirmed diagnosis of IPF
  - HRCT with definite or probable IPF
    - Excluded emphysema >> fibrosis
  - Surgical lung biopsy
- IPF symptoms ≥ 3 months, worsening in past year
Approach to the Diagnosis of ILD: It Often Takes A Village!

Primary Care | Pulmonologists | Radiologists | Pathologists
---|---|---|---
Rheumatologist | Genetics

**Clinical**
- History
- Physical
- Laboratory
- PFTs

**Radiology**
- Chest X-ray
- HRCT

**Pathology**
- Surgical lung biopsy

Multidimensional and multidisciplinary


- Tendency to be overconfident regarding our ability to make a correct clinical diagnosis of IPF-UIP
- Lung biopsy improved the accuracy of the diagnosis

Are Expert Panels Needed To Review All Cases?

- Clinical Panel
- Lung function Panel
- Radiology Panel
- Pathology Panel

Definite or Probable Diagnosis of IPF
Who Should NOT Be Prescribed These Drugs?

- **End stage IPF subjects**, defined by the presence of at least two of the following:
  - TLC < 50% of predicted
  - DLCO, corrected for hemoglobin, <30% of predicted
  - Resting p(A-a) gradient >40 mm Hg
  - O2 desaturation < 80% with exercise (walking on level ground at own pace for 6 minutes) on room air
  - New York Heart Association Class III-IV

How should we assess effectiveness?
Choice of Outcome Measures

• FVC -- $\geq 10\%$ decrease percent predicted FVC
• ABGs -- $\geq 10$ mmHg increase A–a gradient
• Exercise testing – decline in 6MWD from $\geq 50$ m
• Other parameters:
  — Dyspnea (UCSD SOBQ)
  — Quality of life (St George’s Respir. Questionnaire)
  — Changes on HRCT
  — Oxygen use

Has the death rate declined in patients with IPF?
Death Rate in IPF Has Declined?

Demonstrates Mild to Moderate IPF Patients Have a Low Mortality Rate

Placebo patients from INSPIRE and CAPACITY Trials (n=622)
Death Rate in IPF Has Declined?

IPF patients in placebo groups from INSPIRE and CAPACITY Trials (n=622)

% Alive
0 100
60 80
40 60
20 40
0
0 1 2 3 4 5 6 7
Years
UIP
NSIP


New Paradigm for Effective Management of IPF/UIP
**Goals of effective IPF management**

- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent and treat complications
- Prevent and treat exacerbations
- Prevent disease progression
- Reduce mortality

**Cough, Depression, Sleep, Pulmonary rehab., Supplemental Oxygen**

**GERD, Vaccines, PH**

New approaches needed??

- Pirfenidone
- N-acetylcysteine (Fluimucil®)
- Nintedanib
- Sildenafil (advanced disease)

**Lung transplantation**

*These goals should be reached with a minimum of side effects from treatment*

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**Where Do We Go From Here?**

- Role Of Clinical Trials
- Tertiary Referral
### IPF Drugs in the Works

- Biogen: ST 100 (anti integrin αVβ6)
- Bristol-Myers Squibb: Lysophosphatidic Acid Receptor Antagonist NCT01766817
- Centocor: CNTO 0888 (anti-CCL2)
- Fibrogen: FGCL (anti-CTGF) - NCT01890265
- Gilead: Simtuzumab (anti-LOXL2) - NCT01759511
- GlaxoSmithKline: GSK2126458 NCT01725139
- Hoffmann-La Roche: Lebrikizumab NCT01872689
- ImmuneWorks: IW001 NCT01199887

### IPF Drugs in the Works

- MedImmune: Tralokinumab (anti-IL13) - NCT02036580
- Novartis: QAX 576 (anti-IL13)
- Promedior: PRM151 (Petraxin-2)
- Sanofi: SAR156597 (anti IL-4 and IL-13)
- Stromedix: STX-100 - NCT01371305
IPF Drugs in the Works

- Cotrimoxazole - NCT01777737
- Autologous Mesenchymal Stem Cells -NCT01919827
- Inhaled Carbon Monoxide - NCT01214187
- Omeprazole - NCT02085018
- Allogeneic Human Cells (hMSC) - NCT02013700
- Sirolimus NCT01462006

THANK YOU FOR YOUR ATTENTION.