What’s new in IPF drugs?

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Clinical Trial terms

• Phase I: SAFETY (20-100 normal volunteer)
  – Focus on side effects and dosing

• Phase II: Disease specific
  – Focus on dosing and side effects in target population
    • 2a: is it doing what we think
    • 2b: what’s the best dose

• Phase 3: EFFICACY (300-3,000)
  – Does it work?
  – Primary and secondary endpoints

https://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm
ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world.

Explore 256,048 research studies in all 50 states and in 200 countries.

ClinicalTrials.gov is a resource provided by the U.S. National Library of Medicine.

IMPORTANT: Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

Before participating in a study, talk to your health care provider and learn about the risks and potential benefits.

Search (all fields optional)

Condition / Disease: e.g. breast cancer

Other Terms: e.g., NCT number, drug name, investigator name

Country:

Find a study to participate in  Search all studies

Advanced Search
Look for NCT number on all trials

A Phase 2 Study to Evaluate the Safety and Tolerability of PBI-4050 in Patients With Idiopathic Pulmonary Fibrosis (IPF)

This study has been completed.

Sponsor: ProMetic BioSciences Inc.

ClinicalTrials.gov Identifier:
NCT02538536
First Posted: September 2, 2015
Last Update Posted: April 11, 2017

Note that anyone can register a trial, so being on the clinicaltrial.gov website doesn’t prove it’s legitimate!

Try to notice who is sponsoring the trial – academic center? Pharma company?

Will also list inclusion criteria: How old? What PFTs?
https://pulmonaryfibrosisnews.com/

• Treatment-> experimental

“News” from pharmaceutical – so being mentioned here does not imply endorsement from scientific community- but can find published references etc.
Review of recent studies in IPF

Mora..Selman
Nat Rev Drug Discov. 2017
Nov;16(11):755-772.
Take Home

- Lots of promising drugs in the pipeline
- Clinicaltrials.gov should list all potential trials and relevant details
  - Locations of study
  - Inclusion/exclusion
- Local research coordinators will help you look at real-world details
- If not registered with PFF registry and want to be, contact me! kblack1@partners.org
Specific drugs

• Loosely organized by the way the science suggests they would work
• Information from literature or the company’s website
• No endorsement implied!
Targeting the scar

- BMS 986020
- GLPG1690
- FG-3019/pamrevlumab
- Simtuzumab
FG 3019- Pamrevlumab

Basic: Antibody to connective tissue growth factor (CTGF)
Science: CTGF activates fibroblasts
Prior studies: Phase I
Recent Phase II
  – Pts 40-80 with IPF <6 years; FVC >-55%
  – Outcome: change in % predicted FVC over 48 weeks
  – Other outcomes: death, QOL, change in DLCO, hospitalization
  – Company says results promising – stabilization, some improvement

NCT01890265 – sponsor = Pharma
FG 3019 : Pamrevlumab

• Substudy in patients on pirfenidone or nintedanib: “PRAISE” study
  – Reported at ERS conference this year
  – 2.85% decline in pamrevlumab vs 7% placebo
  – Now awaiting results in patients on active drugs
BMS 986020

• **Intro:** Lysophosphatidic Acid receptor 1 (LPA1) Antagonist

• Science: Discovered by Andy Tager to be critical in fibroblast movement and activation
BMS 986020

- Phase I completed in Jan
- Phase II completed Feb 2016
  included: IPF 40-90, no asthma, no improvement over 1 year

Rate of change in forced vital capacity (FVC) over 26 weeks, HRCT changes 6mwt Time Frame

Same drug had liver side effects in scleroderma, so stopped study
GLPG1690

• Intro: inhibits the enzyme “autotaxin” which makes LPA
• Science: Blocking autotaxin mean less LPA to activate fibroblasts
• Data: some efficacy in mice
  – (conflicting data using with other autotaxin inhibitors in mice)

GLPG1690

- Phase I completed 2015
- Phase Ila Study: FLORA trial (3/16-5/17)
- 23 IPF patient (17 on drug, 6 on placebo)
- Primary outcome: safety
- According to press release; those on drug had stable FVC over 12 weeks (reported August 2017) (vs. down very slightly)
Simtuzumab GS-6624

• **Intro:** Humanized antibody against Lysl oxidase-like 2
• **Science:** LOXL2 stabilizes scar tissue in IPF, so blocking that should let scar get softer
• **Data:** Large randomized double blinded phase 2 study (272 pts each group; 183 locations); looked at survival and function
  • **Stopped early:** No effect
  • **New drugs targeting same pathway being developed**

IW-001

• Intro: Oral Antibody to collagen V
• Science: normally collagen V is hidden from immune system, but in pulmonary fibrosis it is exposed and could trigger an immune response; turning that off could help
• Phase 1 in 30 IPF patients (with anti collagen antibodies completed 2012; published 2015

Wilkes Eur Respir J. 2015 May;45(5):1393-402.

NCT01199887
PBI-4050

- Intro “Antifibrotic”
- Science: Tested in mice for ability to reduce known profibrotic factors
- Phase II trial 40 pts across Canada – data presented at ATS 2017
- 9 PBI-4050 only, 15 nintedanib, 16 pirfenidone
  – Pirfenidone blocked absorption of PBI-4050
- Seemed to stabilize patients
- Planning Phase 2/3 trial soon

NCT02538536
Targeting immune system

- Lebrikizumab
- Cotrimoxazole
- Valgancylovir
Lebrikizumab

• Humanized antibody to IL-13
• Science: IL-13 is produced by some T cells of the immune system, and can activate fibroblasts and epithelial cells, so blocking IL-13 could help
• Trialed in asthma as well
• Phase II trial in IPF
  – IPF pts over 40+
  – Skin injections every 4 weeks +/- pirfenidone
  – Started Oct 2013; should be done Nov 15, 2017!

NCT01872689 Hoffmann-La Roche
Cotrimoxazole

- Trimethoprim 80 mg and sulfamethoxazole 400 mg (“Bactrim”)
- Science: infections might contribute to progression; changing “microbiome” may alter disease
- IPF patients have more bacteria in lavage fluid
- ? Role of organism called Pneumocystis jirovecii
- Prior double blind multicenter trial:
  - 181 pts Co-trimoxazole 960 mg (two 480 mg tablets) or bid

Sihulinga Thorax. 2013 Feb;68(2):155-62
Phase 3 trial

Primary Outcome: time to respiratory hospitalization or death

- Other hospitalization, changes in PFTs, # of infections, QOL

Enrolling: IPF >=40, no recent antibiotics
160mg trimethoprim/800mg sulfamethoxazole (double strength twice daily plus folic acid 5 mg daily)
If allergic-> doxycycline

NCT02759120 – sponsored by Weill Medical College of Cornell University
Valganciclovir hydrochloride

• Antiviral drug that works against herpesviruses, CMV
• Science: these viruses mabe promoting diseases
• Phase 1b trial to begin at Vanderbilt
  – single-center, prospective, randomized, placebo-controlled, double-blind pilot study
  – Requires bronchoscopy to test infections

NCT02871401, Vanderbilt and Pharma
Preventing damage

- VAS 2870
- Aeol 10150
- PTL-202
Blocks NAD(P)H oxidases (Nox) that creates reactive oxygen species

Science: Blocking Nox should lower amount of reactive oxygen and decrease fibrotic response

Phase II trial of similar compound **GKT137831** tested in diabetes kidney disease

No human data

Aeol 10150

**Basics:** metalloporphyrin antioxidant,
Like natural enzyme superoxide dismutase
Converts reactive oxygen (O2-) into H2O2

**Science:** oxidative damage to epithelial cells may drive IPF progression

**Indications:** Acute Radiation Sickness, nerve gas damage, IPF, cancer

**Data so far:**

**Preclinical:** tested in mice and macaques against radiation-induced pneumonitis

**Clinical:** Phase I trials (safety) completed (Sep 18 press release)

Tipelukast- MN001

- Oral anti-inflammatory
- Tested for bladder irritation
- Now planning trial
- (also in bladder, liver disease)

PRM-151

- recombinant human serum amyloid P/pentraxin 2 protein
- Science:
  - pentraxin may block activation of inflammatory cells
- Data:
  - Phase II trial published in March 2016
  - 21 pts, safe but not much effect.

NCT01254409, sponsor pharma.

Van dem Blink Eur Respir J. 2016 Mar;47(3):889-97
PTL-202

• Combination of pentoxyfilline and N-acetylcysteine – two approved drugs
• Phase I showed safe; easier to take (only 1/day)
• No efficacy data
New pathways

• PRM 151
• TD 139
• KD025
• RES-529
TD 139

• Intro: Inhaled inhibitor of galectin-3
• Science: Galectin-3 has been shown to be important in recruiting fibroblasts and activating macrophages
• Data: Mice
• Completed Phase 1-2 study in Dec 2016
• (required bronchoscopy to measure drug levels)

NCT02257177
KD025 SLX-2119

• Intro: blocks ROCK2
• Science: blocking signaling pathways might work
• Mouse models show effect

• Phase 2, open-label, 24-week study examines the IPF patients on pirfenidone and/or nintedanib.
• Thirty-six patients: 24 with KD025 at 400 mg QD, 12 patients treated with standard of care

NCT02688647: Sponsor Pharma
RES-529

- Small molecule that blocks TORC1/TORC2 interaction
- Phase I for macular degeneration
- Pre-clinical for glioblastoma
- Pre clinical data about myofibroblast activation
Fentanyl for shortness of breath

- Fentanyl – potent opioid
- Primary trial of inhaled fentanyl: dyspnea (in Ontario)
- Measure breathing
iBio-CFB03

- Basic: Endostatin derived peptide
- Scienc:
  - Endostatin – fragment of a collagen subtype; blocks blood vessel growth
  - Endostatin-like peptides are grown in plants
- Data: mouse of scleroderma and IPF
  - (Dr. Carol Feghali-Bostwick)
- No human data; patent in June 2016

AD-114

Basic idea: new kind of antibody to CXCR4

- CXC chemokine receptor family of GPCRs,
- ligand CXCL12 (also known as stromal cell-derived factor 1, SDF-1)
- Receptor seems to have role in cancers, stabilizing stem cells
- Different antibody structure may bind better
  - variable new antigen receptors ($V_{\text{NAR}}$s) from shark!

- Prior data: No clinical data
  - Plans to be tested in multiple diseases

Exacerbations

• New case report used nintedanib
**Underlying idea:** human recombinant thrombomodulin

- **Science:**
  - anti clotting factor – accelerates thrombin’s activation of protein- > turns off thrombin
  - Thrombin has other pro-fibrotic activity, so reducing it’s activity has potential profibrotic effects

- Approved in 2008 in Japan for treatment of “Disseminated Intravascular Coagulation ("Recomodulin")

ART-120

- Data so far: Prospective study – 22 patients
- Non randomized, single center
- 90 mortality: 36% vs 90%, $P=0.023$; median survival time: not reached vs 15.0 days, $P=0.019$

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Clinical Study of ART-123 for the Treatment of Acute Exacerbation of Idiopathic Pulmonary Fibrosis

Ongoing trial in Japan
multicenter, double-blind, randomized, placebo-controlled, parallel group comparison study
Drug vs. placebo (+ standard of care)
Outcome: survival rate on Day 90 as the primary endpoint
Enrolling: IPF patients 40-80
Expected to complete: in July 2018
Sponsor: Pharma
Lots of reasons for hope!