REFERENCE LIST

SCAN ME

Cochrane Review: Anti-fibrotic Therapy for Idiopathic Pulmonary Fibrosis

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BACKGROUND

- IPF is a progressive interstitial lung disease → causing fibrosis[1]
- Fibrosis → reduce lung function, exercise tolerance[2,3] → death[2,3]
- Early conceptualisation shown no early treatment on antifibrosis[2,3,4]

More recently Pirfenidone and Nintedanib exhibit antifibrosis effects[5,]

Pirfenidone and Nintedanib:
Targets the downstream pathway of fibrogenesis process[3]

However, antifibrosis therapy produced an increased risk of adverse events concomitantly with duration of therapy[6]

***OBJECTIVE**: To summarise all the available randomised controlled trials regarding the efficacy and safety of anti-fibrotic therapy in those with IPF*

METHODS

Participants:
Adults >18 yo. diagnosed with IPF by guidelines and excluding other ILD

Intervention:
Studies comparing antifibrotic agents with placebo or other pharmacological treatment

Studies:
Full text, abstract only, Randomised Controlled Trials

Primary Outcomes:

Mortality; Change in FVC % predicted and ml; Change in exercise tolerance

Secondary Outcomes:

Acute exacerbation; Categorical >10% decline of FVC; Change in diffusing capacity for carbon monoxide (DLCO) (% predicted and mL); Breathlessness, by any validated scale; Cough, Quality of life; Serious adverse events; Adverse events leading to drug discontinuation; Adverse events – Gastrointestinal effects – Neurological – Cardiac – Dermatological – Elevated liver function test abnormalities

Searches for randomised controlled studies on CENTRAL, MEDLINE, EMBASE, CochraneAirways, ClinicaTrials, WHO to June 2021 were performed

PRISMA FLOWCHART

1. Identification:
Records Identified (n=3597)
Duplicate records (n=31)

2. Screening:
Record Screened (n=3565)
Reports Excluded (n=3530)
Reports assessed for eligibility (n=35)

3. Included:
Studies (n=10)
Reports (n=29)

4. Excluded:
Wrong study design (n=5)
Wrong intervention (n=1)

Risk of Bias
Missing Outcome (n=1 moderate)
Selection Bias (n=1 moderate)

RESULTS

Pirfenidone compared to placebo:

- Showed a **non-significant trend** towards mortality (MD: 0.74, 95% CI: 0.5 to 1.1, GRADE: Low)
- **Favoured** change in exercise tolerance (MD: 18.09, 95% CI: 1.13 to 35.06, GRADE: High)
- **Favoured** significantly on change in FVC % predicted (MD: 2.79; 95% CI: 0.87 to 4.71, GRADE: High, MCID Met)
- Showed a **non-significant trend** on change in FVC in ml (MD: 70, 95% CI: -8.87 to 148.87, GRADE: Low).

Nintedanib compared to placebo:

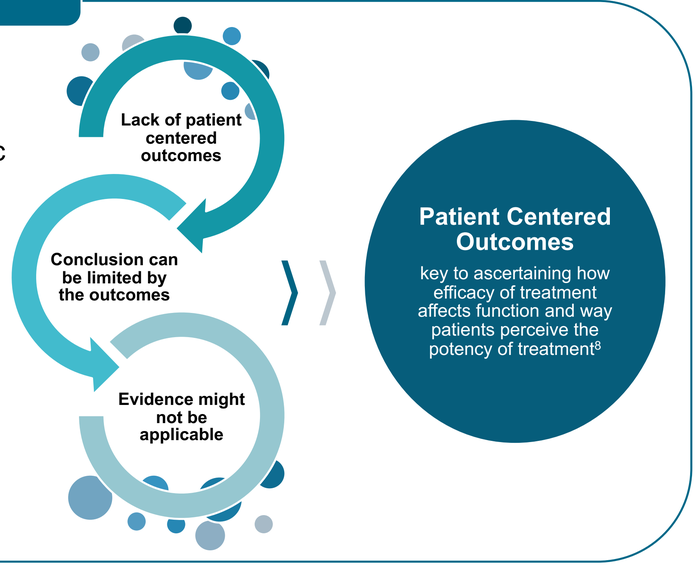
- **Favoured** mortality significantly (MD: 0.47, 95% CI: 0.28 to 0.8, GRADE: Moderate)
- Showed **non-significant trend** in change towards exercise tolerance (MD: 18, 95% CI: -14 to 50, GRADE: Low)
- **Favoured** significantly on change in FVC % predicted (MD: 2.86: 95% CI: 2.51 to 3.2, GRADE: High, MCID Met)
- **Favoured** significantly on change in FVC in ml (MD: 84, 95% CI: 57.52 to 111.23, GRADE: High)

DISCUSSION

Selective geographical and ethnographical sampling
- Pharmacogenetic differences → Genetic polymorphism response to drugs[7]

Inclusion and exclusion criteria limited to certain population – limited applicability
- Studies reported varied criteria (no standard criterion)

Duration of therapy had varied across studies (most of studies had 52 weeks)
- Longer → provided safety evidence
- Shorter → little evidence on mortality



RESULTS

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Pirfenidone
Mortality	1459 (6 RCTs)	⨁⨁◯◯ Low[a,b]	**OR 0.74** (0.50 to 1.10)	86 per 1,000	**21 fewer per 1,000** (41 fewer to 8 more)
Change in FVC % Predicted	1029 (4 RCTs)	⨁⨁⨁⨁ High	-	The mean change in FVC % Predicted was **-8.9**	MD **2.79 higher** (0.87 higher to 4.71 higher)
Change in FVC mL	110 (1 RCT)	⨁⨁◯◯ Low[b,c]	-	The mean change in FVC mL was **-130**	MD **70 higher** (8.87 lower to 148.87 higher)
Change in Exercise Tolerance	953 (3 RCTs)	⨁⨁⨁⨁ High	-	The mean change in Exercise Tolerance was **-77**	MD **18.09 higher** (1.13 higher to 35.06 higher)

GRADE Table of Evidence: Pirfenidone Compared to Placebo

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Nintedanib
Mortality	1858 (6 RCTs)	⨁⨁⨁◯ Moderate[a]	**OR 0.47** (0.28 to 0.80)	104 per 1,000	**52 fewer per 1,000** (72 fewer to 19 fewer)
Change in FVC % Predicted	1546 (7 RCTs)	⨁⨁⨁⨁ High	-	The mean change in FVC % Predicted was **-5.283** % predicted [b]	MD **2.68 % predicted higher** (2.51 higher to 3.21 higher)
Change in FVC mL	1892 (8 RCTs)	⨁⨁⨁⨁ High	-	The mean change in FVC mL was **140.88** [c]	MD **84.37 higher** (57.52 higher to 111.23 higher)
Change in Exercise Tolerance	113 (1 RCT)	⨁⨁◯◯ Low[d,e]	-	The mean change in Exercise Tolerance was **348**	MD **18 higher** (14 lower to 50 higher)

GRADE Table of Evidence: Nintedanib Compared to Placebo

IMPLICATIONS

Practice:

- Pirfenidone: Improves exercise tolerance with risk of adverse events leading to drug discontinuation (GRADE: High)
- Nintedanib: preventing death and better QOL (GRADE: Moderate and High)
- Both: slows progression of FVC decline (GRADE: High and moderate)
- Clinician should monitor risk of adverse event

Research:

- Future directions: Other antifibrotic and other drugs → reverse the effect of fibrosis with less harmful side effects
- Incorporate patient centered outcomes → maximize validity and quality of evidence

Cochrane

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