CO169

Impact of pharmacological interventions on clinical and humanistic outcomes in idiopathic pulmonary fibrosis (IPF): A Systematic Literature Review (SLR)

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Objectives

This SLR aimed to evaluate the impact of approved and emerging therapies on clinical and humanistic outcomes in patients with IPF

Introduction

- IPF is a chronic, progressive, fibrosing interstitial lung disease of unknown cause and is characterised by excessive deposition of extracellular matrix in the interstitium which leads to worsening of lung function, and ultimately to respiratory failure and death, with a median survival or about 3-5 years from diagnosis (1).
- As IPF progresses, lung function declines, dyspnoea and cough worsen, exercise capacity is reduced, and health-related quality of life (HRQoL) deteriorates (2)
- The trajectory of IPF is difficult to predict. It is influenced by the rate of exacerbations, older age, smoking history, lower body mass index, and evidence of advanced physiological and radiographic disease, including a presence of other systemic diseases (3). The two recommended pharmacological antifibrotic (AF) therapies can help reducing lung function decline, slowing the progression of the disease (4, 5)

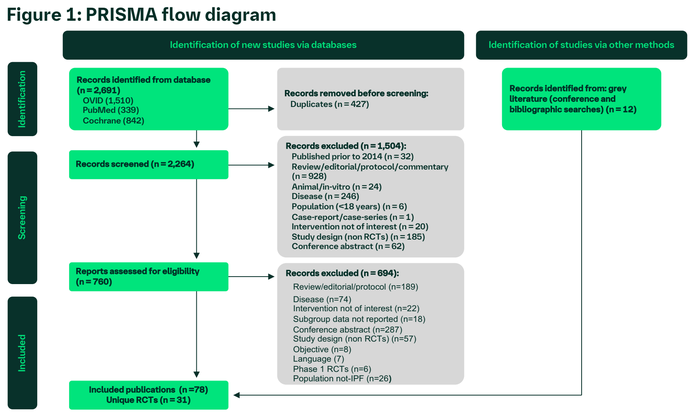
Methods

- Database (MEDLINE®, Embase, PubMed®, Cochrane CENTRAL) and supplementary searches (conference abstracts and HTA websites) were conducted on September 26, 2023, to identify the evidence from Phase II–IV randomised controlled trials (RCTs). Studies assessing the efficacy of various AF mono- and combination therapies on clinical and humanistic outcomes in patients with IPF, published in English between 2011 and 2023, were included with no restrictions on geography
- The SLR followed the Cochrane (6) and PRISMA (7) guidelines and the methodological quality was assessed using the NICE methods (8)
- Key outcomes assessed included forced vital capacity (FVC), diffusing capacity of the lungs for carbon monoxide (DLCO), acute exacerbations (AEs), adverse events, hospitalisation due to respiratory cause, time to death, and health related quality of life (HRQoL)

Results

- In total 31 RCTs (78 publications) met the inclusion criteria (Figure 1); data from secondary publications were assimilated and a single entry was made under the primary publication (PP). Two PPs reported on two separate RCTs each; Richeldi at al. 2014 (9) reported on INPULSIS 1 and 2, while Noble et al. 2011 (10) reported on the CAPACITY 1 and 2 trials

Figure 1: PRISMA flow diagram



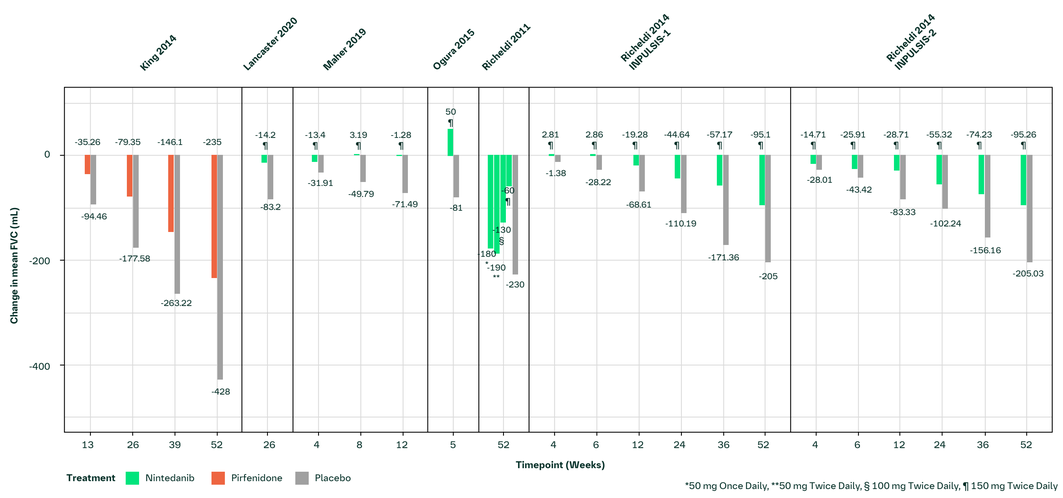
Treatment and comparator groups

- AF monotherapy vs placebo (10 RCTs) with either nintedanib (9, 11-14) or pirfenidone (10, 15, 16) vs placebo
- AF combination therapy vs AF monotherapy/sildenafil/placebo/N-acetylcysteine/lebrikizumab (9 RCTs)
  - Nintedanib + pirfenidone vs NinteN-acetylcysteine vs Pirfenidone danib (17, 18) or vs placebo (14)
  - Pirfenidone + (19), vs Pirfenidone + placebo (20) or vs N-acetylcysteine + Placebo (21)
  - Nintedanib + sildenafil vs Nintedanib + placebo (37)
  - Pirfenidone + sildenafil vs Pirfenidone + placebo (22)
  - Pirfenidone + lebrikizumab vs Pirfenidone + placebo (23)
- Potential IPF treatments vs placebo (N=13): tipelukast (MN-001) (24), GLPG1205 (25), treprostinil (26), CC-90001 (27), pamrevlumab (28), nerandomilast (BI 1015550) (29), PLN-74809 (30), VAY736 + SOC (31), N-acetylcysteine (32), recombinant human pentraxin 2 (PRM-151-202) (33), BMS-986278 (34), BMS-986020 (35), and BMS-986263 (36)

FVC

- Reported in 29 RCTs as: FVC absolute change in mL (25 RCTs), FVC% predicted (22 RCTs), rate of FVC change in mL (11 RCTs), and proportion of patients with FVC response (defined as FVC decline of ≤5 % or ≥5% points, FVC increase of <5 % or >5% points, FVC decline of ≤10% or ≥10% points, FVC increase of ≤10% or ≥10% points, decline in FVC% of predicted value of ≥100 mL and ≥200 mL, or improved or stable FVC) (17 RCTs)
- Nintedanib (9, 11-14) and pirfenidone (15) monotherapies were associated with a lower decline in the mean FVC (mL) compared with placebo at all time points (Figure 2)

Figure 2: Change from baseline in FVC (mL) with AF monotherapies vs. Placebo



*50 mg Once Daily, **50 mg Twice Daily, § 100 mg Twice Daily, ¶ 150 mg Twice Daily

- Compared to placebo, a significantly lower mean change from baseline (CFB) in absolute FVC with nintedanib was reported in the INPULSIS 1 (−95.1 mL vs −205.03 mL; p<0.001), INPULSIS 2 (−95.26 mL vs −205.03 mL, p<0.001) (9) and TOMORROW (−13 vs −230 mL p<0.01) (12) trials and with pirfenidone in the ASCEND trial (−227.96 mL vs −421.91 mL; p<0.001) (15) at 52 weeks (w)
- The mean absolute FVC change was smaller with nintedanib + pirfenidone vs nintedanib alone (−13.3 mL vs −40.9 mL) at 12 w (18)
- Studies reported greater reduction of FVC with pirfenidone + N-acetylcysteine vs pirfenidone alone at 24 w (−112 mL vs −27 mL; p=0.14) (20) and 48 w (−300 mL vs −123 mL; p=0.018) (19) and lower reduction with pirfenidone + N-acetylcysteine vs placebo + N-acetylcysteine at 24 w (−80 mL vs −220 mL; p=0.02) (21)
- There was a greater decline in FVC when combining sildenafil with pirfenidone than with pirfenidone + placebo (−145 mL vs −93 mL; p=0.34) at 52 w (22), but a smaller decline when sildenafil was added to nintedanib relative to nintedanib + placebo (−20.8 mL vs −58.2 mL) at 24 w was observed (37)
- Relative to placebo, significantly lower FVC decline was observed in patients treated with treprostinil at 16w (-106.47 mL vs 35.38 mL; p=0.011) (26), pamrevlumab at 48w (−100 mL vs. −300 mL; p=0.025) (28) and BMS-986020 (−136.27 mL vs −76.6 mL for BMS-986020 600 mg QD and −51.47 mL for BMS-986020 BID ; all p<0.05) at 26 w (35)
- In the INPULSIS trials, nintedanib treatment was associated with significantly greater response and a higher proportion of patients experiencing FVC decline ≤5% points (52.8% and 53.2% for INPULSIS 1 and INPULSIS 2, respectively) vs placebo (38.2% and 39.3%) at 52 w (9). Similarly, a lower proportion of patients experienced a ≥10% categorial change in FVC with pirfenidone compared to placebo (23% vs 27% and 20% vs 35%, for CAPACITY 1 and CAPACITY 2, respectively) at 72 w (10)
- The proportion of patients with improved or unchanged FVC was higher with pirfenidone when compared to either placebo (22.7% vs 9.7%, respectively) (15) or to pirfenidone + N-acetylcysteine (52.8% vs 35.3% (19) and 42% vs 23% (20))

DLCO

- Reported in 18 RCTs as: DLCO% predicted, DLCO mL/min/mmHg, DLCO mmol/min/kPa or proportion (rate) of patients with DLCO response
- Relative to placebo, no significant differences between AF monotherapies with either nintedanib at 52 w (−4.6 mmol/min/kPa vs −4.4 mmol/min/kPa and −3.2 mmol/min/kPa vs −4.8 mmol/min/kPa; all p>0.05, for INPULSIS 1 and INPULSIS 2, respectively) (9) or pirfenidone at 72 w (−7.9% vs −9.9% and −9.8% vs −9.2%; all p>0.05, for CAPACITY 1 and CAPACITY 2, respectively) (10) were found
- The mean CFB in DLCO% predicted in pirfenidone + N-acetylcysteine group was similar to those observed with pirfenidone alone at 48 w (−7.4% vs −10.1%; p=0.517) (19), placebo+ N-acetylcysteine at 48 w (−2.8% vs −4.4% at 48; p= w0.53) (21) and pirfenidone + placebo at 24 w (−2.1% vs −2%; p=0.73) (20)
- Similarly, among emerging therapies, no significant differences were found in DLCO change between placebo and nerandomilast at 12 w (29), GLPG1205 at 26 w (25), BMS-986020 at 26 w (35), PRM-151 at 28 w (33), N-acetylcysteine at 60 w (32), VAY736 + SOC at 48 w (31), and BMS-986263 at 24 w (36)

Other outcomes

AEs (nine RCTs):

- Treatment with nintedanib lowered the AE rate relative to placebo with a significant benefit in prolonging time to first AE reported in the INPULSIS 2 (HR 0.38, 95%CI 0.19-0.77; p=0.005); the proportion of patients with AEs was 3.6% (vs placebo [9.6%]) and 6.1% (vs placebo [5.4%]) at 52 w for the INPULSIS 1 and INPULSIS 2 trials, respectively (9)
- Pirfenidone alone resulted in higher AE rates compared to pirfenidone + N-acetylcysteine (11.1% vs 2.9%) at 48 w (19), and lebrikizumab + pirfenidone (6.31% vs 2.9%) at 122 w (23), but nintedanib and nintedanib + sildenafil were found to have comparable rates (7.4% vs 7.3%) at 24 w (37)
- Compared to placebo, the AE rates were similar in patients treated with N-acetylcysteine (32), and tipelukast (24)

Hospitalisations due to respiratory causes (six RCTs):

- During the 26 w treatment, no hospitalisations were reported for the nintedanib group compared with a 7% rate in the placebo group (11)
- Relative to pirfenidone, comparable hospitalisation rates with lebrikizumab + pirfenidone after 122 w (14.5% vs 15.4%) (23) and with pirfenidone + sildenafil after 52 w (45% vs 40%) were observed, in addition to similar times to respiratory hospitalisations (22)
- Relative to placebo, across patients treated with other therapies, the respiratory-related hospitalisation rates were similar and ranged from 2.8% with GLPG1205 vs 4.3% with placebo after 26 w (25), to 10% with pamrevlumab vs 13.2% with placebo after 55 w (28)

Respiratory-related mortality (eight RCTs) and Time to death (two RCTs):

- Respiratory related death rate (52w) with AF monotherapies ranged from 2.35% (12) to 4.3% (9) across nintedanib (150 mg BID) groups, and from 4.9 % (9) to 9.4% (12) across placebo groups
- At 52 w, no significant difference was observed between pirfenidone + placebo vs either pirfenidone + lebrikizumab (HR 0.42, 95%CI 0.17–1.04) (23) for all-cause mortality or vs pirfenidone + sildenafil (HR 0.76, 95%CI 0.38–1.50 and HR 0.67, 95%CI 0.31–1.47; all p>0.05 for all-cause and respiratory related mortality, respectively) (22)

Adverse events (31 RCTs):

- Consistent across all the studies, treatment groups exhibited a slightly higher incidence of any adverse event vs placebo; at 52 w similar incidence between AF monotherapies (90.7–96.6%) and placebo (88.7–90.6%) were reported
- The proportion of patients with adverse events ranged from 81% to 98% with nintedanib and 64% to 90% with placebo (9, 11-13)
- Diarrhoea was the most frequent adverse event in the nintedanib groups (61.5–63.2%) vs placebo (18.3–18.6%) (9); gastrointestinal and skin-related adverse events were more frequent across pirfenidone than placebo groups (10, 15)

HRQoL (22 RCTs):

- In total, 22 RCTs (9-12, 15, 17-25, 27, 29, 32, 35, 37, 38) assessed HRQoL using St. George's Respiratory Questionnaire (SGRQ), San Diego Shortness of Breath Questionnaire (SOBQ), EuroQol- 5 Dimension (EQ-5D) questionnaire, the Living with Pulmonary Fibrosis (L-PF) questionnaire, Modified Medical Research Council (mMRC), Hospital Anxiety and Depression Scale (HADS), Chronic obstructive pulmonary disease Assessment Test (CAT), A Tool to Assess Quality of Life in IPF (ATAQ-IPF), Patient Global Impression of Change (PGIC), Hogan Development Survey (HDS), and the Cough and Sputum Assessment Questionnaire (CASA-Q) following various treatments. In general, no meaningful improvements in HRQoL were observed
- In patients treated with AF monotherapy or placebo, the CFB in SGRQ scores at 52 w was 11.4 with pirfenidone (22) and ranged from −3.12 (11) to 4.6 (12) with nintedanib, and 4.3 to 5.5 with placebo (9)

Conclusions

- Approved AF monotherapies, their combination, including combination with other therapies have shown to slow disease progression to various extents. Limited impact on HRQoL was observed, and adverse events were common, with gastrointestinal being the most frequent adverse events
- Pharmacological research has intensified in the pursuit of innovative targeted molecules (targeting e.g. alveolar macrophages, fibroblasts or epithelial cells) that could meet patients' needs for more efficient and well-tolerated IPF treatments

Abbreviations

AE, acute exacerbations ; AF, antifibrotic; CFB, change from baseline; DLCO, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; HRQoL, health related quality of life; PP, primary publication

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