Treatable traits in idiopathic pulmonary fibrosis: focus on respiratory tract infections—a systematic review and a meta-analysis

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Summary

Background Idiopathic pulmonary fibrosis (IPF) is a progressive, deadly lung disease with several factors, including respiratory tract infections (RTI), for disease worsening. There's no comprehensive data on RTI incidence in IPF patients across different therapies, including antifibrotic (nintedanib or pirfenidone), investigative or placebo treatments.

Methods A systematic search of databases Medline, EMBASE, Cochrane Central, Web of Science and Scopus was conducted on September 30th 2024 (PROSPERO registration number: CRD42023484213). Only randomized controlled trials of drugs intended for IPF treatment in adults and reporting RTI incidence were included. Pooled risk ratio with 95% confidence interval (CI), risk of bias, GRADE and CINEMA assessments were conducted along with subgroup analyses for upper and lower RTI and for different antifibrotic doses.

Findings A total of 27 trials of different drugs aimed for IPF therapy were pooled in a pairwise meta-analysis, 11,542 patients were analyzed with an overall number of 4156 RTI events, representing an average incidence of 38.4 ± 23.5%. Most therapies did not affect RTI risk in IPF, although single trials with everolimus and trimethoprim/sulfamethoxazole showed a significant decrease compared to placebo. For antifibrotics, RTI incidence was similar with pirfenidone treatment compared to nintedanib (RR: 0.98 CI: [0.71; 1.36]) and compared to placebo (RR: 0.88 CI: [0.69; 1.10]) and nintedanib compared to placebo (RR: 0.89 CI: [0.71; 1.12]).

Interpretation RTIs are frequently reported adverse events in IPF patients over a one-year period, with different investigated treatments showing no profound impact compared to placebo. Future clinical trials should focus on targeting treatable traits like RTIs.

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Keywords: Idiopathic pulmonary fibrosis; Respiratory tract infection; Pirfenidon*; Nintedanib; Safety; Meta-analysis; Network; RTI; IPF

Introduction

Idiopathic pulmonary fibrosis (IPF) is a rare, progressive, fatal interstitial lung disease (ILD).[1] Due to its relative abundance and well-described clinical-radiological-pathological features, it can be considered the benchmark disease for progressive ILDs.[1] Although the exact etiology of the disease is not known, several factors are known to contribute to the development and

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Research in context

Evidence before this study

Idiopathic Pulmonary Fibrosis (IPF) is a rare and fatal disease with an extremely poor prognosis and no effective drug treatments currently available. Various factors—like respiratory tract infections (RTIs)—contribute to the rapid progression of IPF. Since IPF cannot be reversed, the focus has shifted to identifying and managing treatable traits as the main approach for treatment and research.

Added value of this study

All placebo-controlled interventional clinical trials recruiting IPF patients for at least one year were included. All studies comprised 11,542 patients and RTIs were very common (average incidence 38.4 ± 23.5%). Most therapies did not change, but everolimus and trimethoprim/sulfamethoxazole reduced RTI incidence compared to placebo. The actual standard of care with the antifibrotics pirfenidone or nintedanib did not change the incidence of RTI over the one-year period, confirming safety of these treatments irrespective of the dose used.

Implications of all the available evidence

As RTIs were reported frequently in all patients with IPF, including those on antifibrotic treatment (38.9 ± 9.5%), long-term follow-up in real world is necessary to assess interventional measures for this treatable pulmonary trait in the long term.

progression of IPF, including infections, smoking, pollution, chronic aspiration, genetic predisposition, and drug toxicity.[2–4]

Nevertheless, specific genetic and host susceptibility factor(s) responsible for determining the phenotypic expression and clinical manifestations of IPF are still unidentified.[3] Pathological features result from abnormal proliferation of fibrous tissue and remodeling due to abnormal function and signaling of alveolar epithelial cells and interstitial fibroblasts.[1]

Today, there is no medication available to cure IPF. However, two approved drugs are used in clinical practice to slow progression, reduce functional decline (forced vital capacity–FVC) and overall mortality: nintedanib and pirfenidone.[1,4–6] These therapies were also effective in real-world datasets despite including more severe cases and multimorbid populations mostly excluded from clinical trials.[7–12]

Several factors act as triggers for the worsening of IPF, and treatable traits are important factors where effective therapy might reduce progression. These lung-specific treatable traits include smoking cessation, treatment of secondary pulmonary hypertension, treating gastroesophageal reflux and subsequent aspiration, prevention of infections by vaccination measures and adequate management of curable infections that co-exist with the underlying disease.[13–19]

Respiratory tract infections (RTIs) are amongst the most common illnesses associated with high mortality rates, especially in patients with underlying lung disease.[20–23] RTIs can trigger acute exacerbations of a number of chronic lung diseases, often leading to hospitalization[23] or admission to intensive care unit.[22,24] Reducing the incidence of treatable traits, including RTIs, might be associated with a better long-term outcome in IPF.[19,21,22,25,26]

Previous investigational IPF treatments did confirm differences in their safety profile. Therefore, a rigorous, objective and systematic quality evaluation of their impact on treatable traits, including RTIs, should be investigated. This study collected all RCTs of IPF with a duration of least one year and used a systematic review and meta-analysis method for different investigated drugs on the incidence of RTI as compared to placebo-treated patients.

Methods

We report our systematic review, pairwise and network meta-analyses in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Supplementary Table S1).[27]

The review protocol was registered on the PROSPERO International Prospective Register of Systematic Reviews (CRD42023484213). We did not deviate from the previously designed protocol.

Search strategy

A systematic search was performed in five scientific databases — Medline (via PubMed), Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus and Web of Science — for studies published from inception to the date of the search, 30th of September 2024. The following search key was used in all databases without any other filters or restrictions on language, date, type, or content: ((“idiopathic” AND “pulmonary” AND “fibrosis”) OR (“cryptogenic” AND “fibrosing” AND “alveolitis”) OR “CFA” OR “IPF”) AND (“nintedanib” OR (“BIBF” AND “1120”) OR pirfenidon* OR “antifibrotic” OR “esbriet” OR “ofev” OR (“tyrosine” AND “kinase” AND “inhibitor”) OR “TKI”). Reference lists of eligible and cited articles (via Google Scholar search engine and Citationchaser) were also screened to capture all relevant studies.[28]

Selection and eligibility criteria and data extraction

After automatic and manual removal of duplicate records using the reference management software

EndNote 21 (Clarivate Analytics, Philadelphia, PA, USA), three review authors (Zs.M. & A.B. and Cs.G.) independently screened titles and abstracts and then full texts against predefined eligibility criteria (Zs.M. screened the total pool of records, A.B. and Cs.G. screened 50% each of the records). Cohen's kappa was calculated for title-abstract and full text selection to assess agreement between Zs.M, A.B and Cs.G during the selection process (0.98 and 0.95 respectively).[29] A third review author (C.T.) resolved conflicts. Inclusion criteria specified any RCTs that reported incidences of RTIs with confirmed IPF, comparing any drug for IPF treatment to placebo. We excluded animal experiments, studies on children, or studies with a duration of less than 52 weeks in order to exclude seasonal effects. Additionally, non-placebo-controlled RCTs were excluded from the network meta-analysis. Two authors (Zs.M. & A.B.) independently but in parallel collected the following data in a standardized data collection sheet: trial and baseline patient characteristics including authors, year of publication, digital object identifier, study site, study design, age, sex at birth distribution, follow-up time, number of patients in exposure and control groups, incidence of RTIs, if upper (U) and lower (L) RTIs were available. Any disagreements on data collection were resolved by a third review author (C.T.).

Statistical analysis

The manuscript utilized two meta-analytic approaches: multilevel pairwise, and network meta-analysis.

For the pairwise meta-analysis, a multilevel random-effects model was used, with study ID set as a random factor (as suggested by Viechtbauer (2021)[30]) to pool effect sizes. Multilevel model was used in pairwise comparisons accounted for the possible correlations between within-study shared control groups as suggested by Van den Noortgate et al.[31] and following the methodology of Assink et al.[32] Relative risks (RRs)—calculated from the number of events (incidence of RTIs) and the total number of patients in the RTI in treatment groups and placebo or standard of care (SOC) groups—were used for effect size measure with a 95% confidence interval (CI).

Results were considered statistically significant if the pooled CI did not contain the null effect line (at the value of 1 for RRs). We summarized the findings from the meta-analysis in forest plots. Where applicable, prediction intervals were reported.

Between-study heterogeneity was described by the Higgins&Thompson's I^2 statistics.[33] Small study publication bias was assessed by visual inspection of funnel-plot and by Egger's test,[34] with a preset p-value of 0.1.

For the network meta-analysis, we used a random-effects model to calculate the p-score for the overall ranking of the currently used antifibrotic drugs on the incidence of RTI. We calculated pooled RRs with 95% CI, assessing the overall incidence of RTIs in the treatment groups. Subgroup analyses were performed for currently used antifibrotics based on dose and site of respiratory infections (e.g., URTI and LRTI).

All statistical analyses were performed with R[35] using the meta[36] package for basic meta-analysis calculations and plots, package metafor[37] for multilevel models, and packages netmeta[38] and pairwise[39] for the network meta-analysis.

Risk of bias assessment and confidence rating

Based on the recommendations of the Cochrane Collaboration,[40] two independent review authors (Zs.M. & A.B.) used the RoB-2 tool (ROB2 IRPG beta v7 2020) to assess the quality of the studies included.[41] A third review author (C.T.) resolved the conflicts.

Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) was used to evaluate the level of certainty of evidence for the outcomes of pairwise meta-analyses.[42] Similarly, the confidence rating of indirect and direct comparisons in the network meta-analyses was assessed with Confidence in Network Meta-Analysis (CINEMA).[43]

Role of funding source

No funding was received for the creation of this manuscript, including the associated tests, analyses and writing process.

Results

Results of search and selection

The selection process is detailed in the PRISMA flow chart (Fig. 1). We identified a total of 18,085 records, 27 of which were included in pairwise comparisons.

Characteristics of the included studies

The characteristics of the 27 randomized control trials included in the pairwise comparisons are presented in Table 1. Twenty were international, and seven were single-country studies. A total of 7 studies with 3094 patients were performed with the currently used standard of care antifibrotic drugs nintedanib or pirfenidone (3 and 4 RCTs; 981 and 874 IPF patients, respectively). We included 7 studies with 1268 patients treated with different antibodies and 13 studies with 4111 patients investigating other drugs in the exposure group. The mean age of patients in the exposure group ranged from 58.0 to 72.4 years, and patients were predominantly male (76.0 ± 9.3%)

Pairwise comparisons

On the basis of a 52-week treatment period, nintedanib and pirfenidone therapy were associated with a non-significantly reduced risk of the incidence of RTIs by 13% (RR: 0.87 CI: [0.63; 1.21]) and 14% (RR: 0.86 CI: [0.62; 1.20]), respectively (Fig. 2). Looking at the

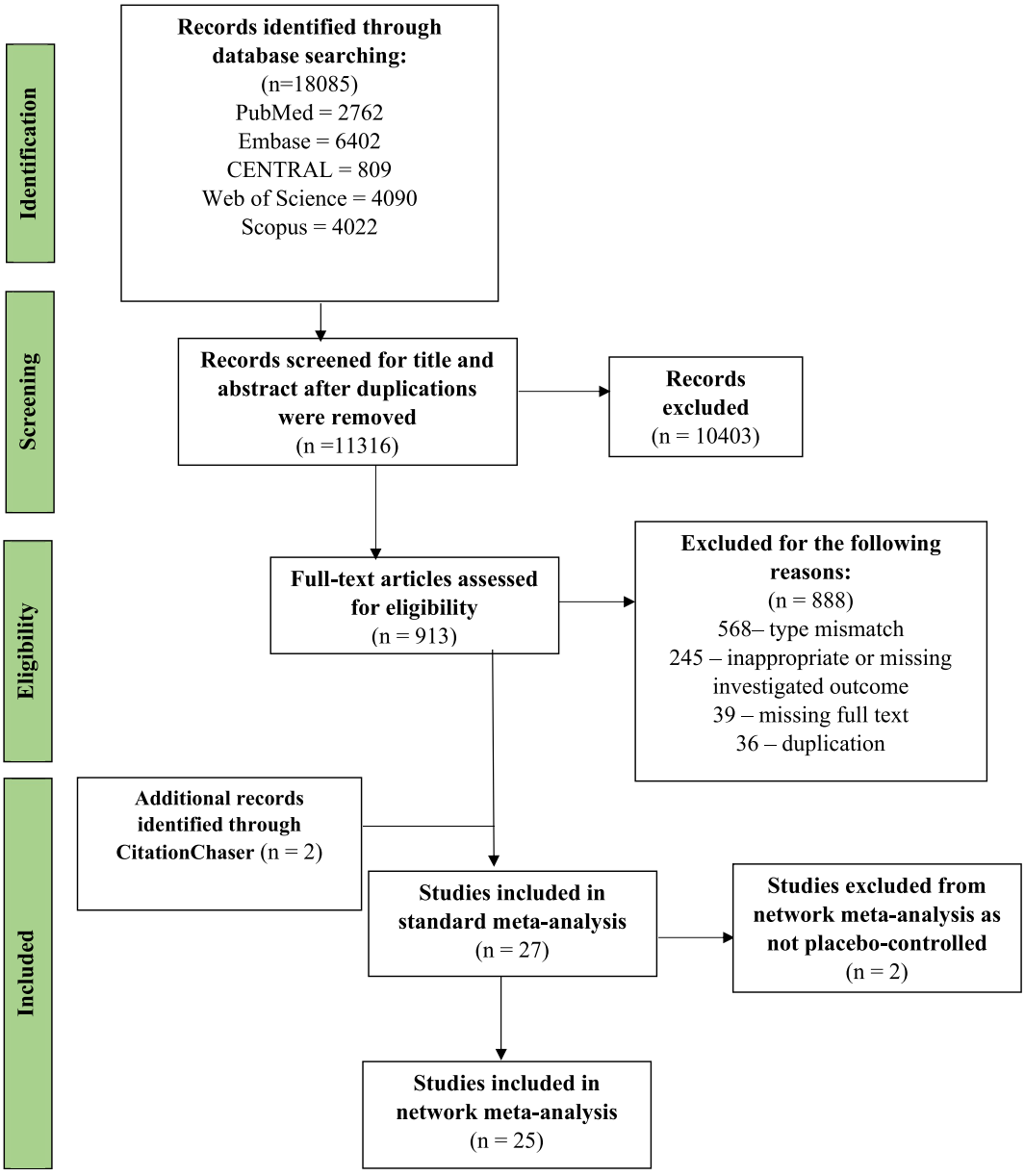

Fig. 1: **Preferred reporting in systematic reviews and meta-analyses (PRISMA) flowchart showing the selection process.**

individual RCTs, in one of the 300 mg/day nintedanib trials, we found that treatment with the antifibrotic drug was associated with significantly decreased RTI incidence (RR: 0.63 CI: [0.40; 0.98])[48] whereas the other showed no changes as compared to placebo.[44] Pirfenidone administered at a dose of 1800 mg/day was associated with a reduced RR for the incidence of RTIs (RR: 0.68 CI: [0.55; 0.85]); however, this study included only patients from a single country.[45]

In RCTs assessing antibodies for IPF treatment, the overall risk of RTI was slightly increased, with a significant reduction associated with simtuzumab (monoclonal anti-LOXL2 antibody) 125 mg/week (RR: 0.86 CI: [0.78; 0.95]).[51] On the other hand, using romilkimab (anti-IL-4 and anti-IL-13 antibody) at a dose of 200 mg every two weeks was associated with a significantly increased incidence of RTI (RR: 1.30 CI: [1.05; 1,61]).[65] Among other drugs, trimethoprim/sulfamethoxazole in one of three trials (RR: 0.50 CI: [0.37; 0.68])[64] everolimus (mTOR inhibitor) (RR: 0.47 CI: [0.33; 0.65])[55] and interferon γ-1b (RR: 0.93 CI: [0.88; 0.99]) were associated with a significant reduction in the risk of the incidence of RTI compared to placebo.[62]

Author (publication year)	Study ID	Country	Centres	Drug used	Dose	Age (years)		No of patients (female %)		RTI reported (%)		FVC (% predicted)	
						Exposure	Control	Exposure	Control	Exposure	Control	Exposure	Control
L. Richeldi (2014)[44]	INPULSIS-1	International	205	Nintedanib	300 mg/d	66.9 ± 8.4	66.9 ± 8.2	309 (18.8)	204 (20.1)	103 (33.3)	80 (39.2)	79.5 ± 17	80.5 ± 17.3
L. Richeldi (2014)[44]	INPULSIS-2	International	205	Nintedanib	300 mg/d	66.4 ± 7.9	67.1 ± 7.5	329 (22.2)	219 (21.9)	109 (33.1)	75 (34.2)	80.0 ± 18.1	78.1 ± 19.0
H. Taniguchi[45]	H.Taniguchi–2010	Japan	73	Pirfenidone	1800 mg/d	65.4 ± 6.2	64.7 ± 7.3	109 (21.3)	107 (22.1)	55 (50.5)	79 (73.8)	77.3 ± 16.8	79.1 ± 17.4
					1200 mg/d	63.9 ± 7.5		55 (14.5)		33 (60.0)		76.2 ± 18.7	
T. E. King (2014)[46]	ASCEND	International	127	Pirfenidone	2403 mg/d	68.4 ± 6.7	67.8 ± 7.3	278 (20.1)	277 (23.1)	133 (47.8)	122 (44.0)	67.8 ± 11.2	68.6 ± 10.9
P.W. Noble (2011)[47]	CAPACITY 004	International	110	Pirfenidone	2403 mg/d	65.7 ± 8.2	66.3 ± 7.5	174 (32.0)	174 (26.0)	8 (4.6)[a]	10 (5.7)[a]	74.5 ± 14.5	76.2 ± 15.5
					1197 mg/d	68 ± 7.6		87 (25.0)		7 (4.1)[a]		76.4 ± 14.4	
P.W. Noble (2011)[47]	CAPACITY 006	International	110	Pirfenidone	2403 mg/d	66.8 ± 7.9	67.0 ± 7.8	171 (28.0)	173 (28.0)	7 (4.1)[a]	12 (6.9)[a]	74.9 ± 13.2	73.1 ± 14.2
L. Richeldi (2011)[48]	TOMORROW	International	92	Nintedanib	50 mg/d	65.3 ± 9.4	64.8 ± 8.6	86 (24.4)	85 (25.9)	29 (33.7)	35 (41.2)	79.8	77.6
					100 mg/d	64.9 ± 8.5		86 (27.9)		34 (39.5)		80.4	
					200 mg/d	65.1 ± 6.6		86 (24.4)		35 (40.7)		83.0	
					300 mg/d	65.4 ± 7.8		85 (23.5)		22 (25.9)		78.1	
L. Richeldi (2019)[49]	PRAISE	International	39	Pamrevlumab	30 mg/kg/3 weeks	68.3 ± 7.1	68.4 ± 7.2	50 (34.0)	53 (19.0)	34 (68.0)	30 (56.6)	74.5 ± 11.9	73.1 ± 11.1
T. M. Maher (2021)[50]	RIFF	International	156	Lebrikizumab	250 mg/4 weeks	70 [51; 88]	69 [52; 84]	78 (16.9)	76 (17.1)	32 (41.0)	32 (42.1)	73.0 [38.0; 98.8]	72.8 [39.0; 99.4]
				Lebrikizumab + Pirfenidone	250 mg/4 ws+ ≤2403 mg/d Pirfenidone	69 [52; 85]	69.0 [50; 86]	174 (21.3)	177 (19.1)	75 (43.1)	71 (40.1)	71.5 [42.8; 101.2]	73.4 [39.7; 98.3]
G. Raghu (2016)[51]	RAINIER	International	183	Simtuzumab	125 mg/w	67.7 ± 7.6	68.5 ± 7.1	272 (16.0)	272 (17.0)	184 (67.6)	214 (78.7)	61.4 ± 12.2	62.3 ± 12.2
F.J. Martinez (2021)[52]	CLEANUP-IPF	USA	35	TMP/SMX	1920 mg/d + 5 mg/d Folic acid	71.0 {66.9; 76.3}	72.1 {67.7; 76.1}	128 (23.6)	259 (19,7)	2 (1.6)	5 (3.5)	68.9 {56.7; 81.8}	71.2 {57.4; 83.8}
				Doxycyclin	<50 kg: 100 mg/d; ≥50 kg: 200 mg/d			126		3 (2.4)	2 (1.7)		
C.E. Daniels (2010)[53]	Daniels–2010	USA & Mexico	13	Imatinib	600 mg/d	66.0 [47; 97]	67.8 [52; 79]	59 (22)	60 (36.0)	8 (13.6)[b]	15 (0.25)[b]	64.4	65.6
M. Demedts (2005)[54]	Demedts–2005	International	36	ACC	1800 mg/d	62.0 ± 9.0	64 ± 9.0	80 (31)	75 (25.0)	33 (44.3)	42 (56.0)	N.A.	N.A
M.A. Malouf (2011)[55]	Monique–2011	Australia	6	Everolimus	8 mg/d	58.0 ± 9.0 [38; 75]	60 ± 9.0 [39; 75]	44 (36)	45 (29.0)	44 (17.7)	64 (38.1)	65 ± 15 [34; 100]	69 ± 20 (25; 102)
A.M. Wilson (2020)[56]	EME-TIPAC	UK	39	TMP/SMX	1920 mg/d + 5 mg/d Folic acid	71.9 ± 7.8	70.7 ± 7.1	169 (18.3)	172 (8.7)	63 (9.1)	66 (10.3)	56.2 ± 8.9	55.2 ± 10.0

(Table 1 continues on next page)

Author (publication year)	Study ID	Country	Centres	Drug used	Dose	Age (years)		No of patients (female %)		RTI reported (%)		FVC (% predicted)	
						Exposure	Control	Exposure	Control	Exposure	Control	Exposure	Control
(Continued from previous page)													
T.M. Maher (2023)[57]	ISABELA-1	International	106	Ziritaxestat	600 mg/d	69.4 ± 7.2	70.6 ± 7.7	174 (18.4)	174 (16.1)	29 (16.7)	25 (14.4)	80.4 ± 17.5	79.7 ± 15.9
					200 mg/d	70.0 ± 6.7		175 (18.3)		30 (17.1)		77.9 ± 18.1	
T.M. Maher (2023)[57]	ISABELA-2	International	106	Ziritaxestat	600 mg/d	69.2 ± 7.2	70.6 ± 6.6	259 (19.3)	258 (19.0)	49 (18.8)	34 (13.1)	76.5 ± 16.8	77.6 ± 17.2
					200 mg/d	69.7 ± 7.3		260 (18.1)		49 (18.9)		77.7 ± 15.5	
K. Kataoka (2023)[58]	FITNESS	Japan	19	Rehabilitation	–	71.2 ± 4.9	40.4 ± 5.5	45 (20)	43 (23.0)	5 (11.1)	3 (6.9)	72.8 ± 14.5	75.0 ± 12.9
J.M. Parker (2017)[59]	Parker–2017	International	48	Tralokinumab	800 mg/d	67.9 ± 6.7	67.5 (6.1)	59 (22)	57 (21.1)	39 (66.1)	32 (56.1)	70.6 ± 13.4	70.3 ± 12.0
					400 mg/d	67.3 ± 7.7		57 (26.3)		40 (70.2)		68.5 ± 14.3	
G. Raghu (2013)[60]	MUSIC	International	48	Macitentan	10 mg/d	66 [37; 84]	64.0 [49; 81]	119 (29.4)	59 (37.3)	42 (35.3)[b]	23 (38.9)[b]	76.1 [47.7; 121.1]	73.8 [54.0; 126.4]
T.E. King (2011)[61]	King–2011	International	119	Bosentan	250 mg/d	63.8 ± 8.4	63.2 ± 9.1	407 (17.3)	209 (36.4)	294 (72.4)	165 (78.9)	74.9 ± 14.8	73.1 ± 15.3
T.E. King (2009)[62]	INSPIRE	International	81	Interferon-γ-1b	600 ug/w	66 ± 7.7	65.9 ± 7.9	551 (28)	275 (32.0)	449 (81.5)	240 (87.3)	72.2 ± 12.3	73.1 ± 13.4
G. Raghu (1991)[63]	Raghu–1991	USA	2	Azathioprine	25 mg/d	58.0 ± 2.0	54.0 ± 3.0	14.0 (64)	13 (46.0)	2 (7.1)	0 (0)	70.0 ± 4.0	65.0 ± 4.0
L. Shulgina (2012)[64]	Shulgina–2012	UK	28	TMP/SMX	1920 mg/d + 5 mg/d Folic acid	72.4 ± 8.5	70.7 ± 8.6	95 (30.5)	86 (24.4)	33 (34.7)	60 (69.8)	70.0 ± 21.5	71.5 ± 21.0
G. Raghu (2018)[65]	Raghu–2018	International	N.A.	Romilkimab	200 mg/w	68 ± 7.6	69 ± 8.6	108 (25)	110 (20.0)	55 (50.9)	59 (54.1)	68.9 ± 16.0	71.5 ± 16.0
					200 mg/2 ws	67.4 ± 7.2		109 (29.4)		76 (70.4)		70.3 ± 17.8	
L. Richeldi (2024)[66]	STARSCAPE	International	275	Zinpentraxin-α	10 mg/kg/4 ws	70.8 ± 7.3	70.5 ± 7.6	331 (18.2)	329 (20.9)	96 (29)	92 (28)	77.9 ± 16.5	77.1 ± 17.1
G. Raghu (2024)[67]	Zephyrus-1	International	117	Pamrevlumab	30 mg/kg/3ws	70.2 ± 7.8	70.8 ± 7.0	181 (27.1)	175 (28.0)	71 (39.2)	57 (32.6)	69.6 ± 11.6	71.8 ± 11.5

RCT—randomized controlled trial; w—week; ws—weeks; d—day; TMP/SMX—trimethoprim/sulfamethoxazole; ACC—acetylcysteine; FVC—forced vital capacity; UK–United Kingdom; USA–United States of America; N.A.—data not available; mean ± SD; or median [range min; range max;] or median {IQRmin; IQRmax}; iRTI—incidence of respiratory infections; IQR—interquartile range. [a]Only serious adverse events were reported. [b]Pneumonia was reported as serious adverse event.

Table 1: **Characteristics of the included studies.**

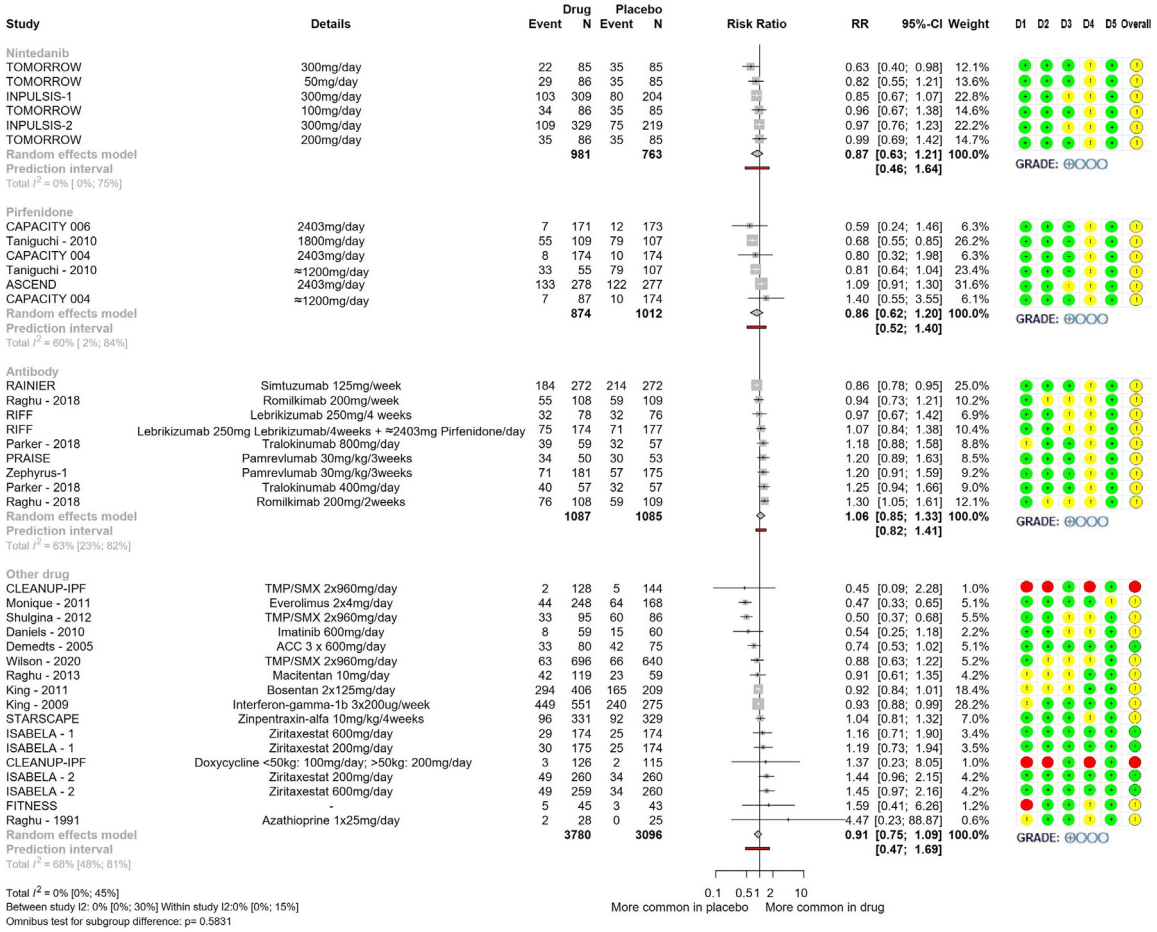

Fig. 2: **Pairwise comparisons of different treatments–intended to treat IPF–to placebo for the incidence of RTI in IPF with a duration of at least 52 weeks, assessed with RoB and GRADE.** Abbreviations: RoB—risk of bias; RR—relative risk; CI—confidence interval. Risk of bias is assessed on a scale from low risk to high risk. Green dots—low risk of bias; yellow dots: some concerns in risk of bias; red dots: high risk of bias; GRADE is assessed on a scale from 1 to 4, lowest to highest evidence certainty level, respectively.

Methodological quality and risk of bias and publication bias of pairwise meta-analysis

For two RCTs,[52,58] the risk of bias was high due to the lack of conclusive data on randomization and the difficulty in assessing and reporting adverse events (AE). In the other case, the article did not clearly state the exact process of randomization, and blinding was not feasible.[58] A low risk of bias was reported in five cases, and some concerns were observed in the other cases (Fig. 2). Due to the majority of RCTs with some concerns at the risk of bias assessment, as well as the high degree of inconsistency and overall imprecision, the result of the GRADE assessment is very low evidence of certainty for all included studies (Fig. 2). Publication bias was analyzed with funnel plots. Our analysis and the calculated Egger's test showed that there was no significant publication bias for our included studies (Supplementary Fig. S1).

Network meta-analysis

Comparison of currently approved antifibrotics regardless of dosage

We analyzed 7 studies with 3094 IPF patients receiving nintedanib or pirfenidone treatment. The total number of events was 988. The network plot is shown in Supplementary Fig. S2. On the basis of a 52-week treatment period and our direct and indirect comparisons, pirfenidone and nintedanib were associated with a non-significantly reduced RR for the incidence of RTIs by 12% and 11%, respectively, compared to placebo. The RR for the incidence of RTIs was similar (RR: 0.98 CI: [0.71; 1.36]) with pirfenidone treatment compared to nintedanib. In all our comparisons, the 95% CI overlapped between groups (Table 2). The overall ranking of drugs by their effect on the incidence of RTIs is shown in the supplement (Supplementary Table S2).

Pifenidone	–	0.88 [0.69; 1.10]
0.98 [0.71; 1.36]	**Nintedanib**	0.89 [0.71; 1.12]
0.88 [0.69; 1.10]	0.89 [0.71; 1.12]	**Placebo**

The upper triangle part of the league table contains estimates based on direct comparisons, whereas the lower triangle shows estimates based on direct and indirect comparisons. RR [CI].

Table 2: **Direct and indirect comparisons of currently used antifibrotic drugs in IPF by RTI incidence.**

We performed a sensitivity analysis for two trials[47] to reduce our reporting bias because these studies reported only serious RTIs as adverse events. Inclusion or exclusion of these RCTs had no notable impact on the statistical outcomes of our results (pirfenidone–nintedanib: RR: 0.98 (CI: [0.71; 1.36])—RR: 1.00 (CI: [0.69; 1.44]); pirfenidone vs. placebo: RR: 0.88 (CI: [0.69; 1.10])—0.89 CI: [0.70; 1.14]; nintedanib–placebo: 0.89 (CI: [0.71; 1.12])—0.89 (CI: [0.68; 1.17]).

Subgroup analyses

For dose dependency in this subgroup, a network meta-analysis included 7 RCTs with 3094 patients receiving nintedanib or pirfenidone treatment. There was a total of 988 events in this subgroup network analysis. The network plot is shown in Supplementary Fig. S3.

Patients treated with pirfenidone 1800 mg/day had a significantly lower RR (0.71 CI: [0.51; 0.99]) of RTI incidence for one year, than patients on placebo in the RCT including patients from Japan.[45] No other clinically relevant and statistically significant differences were found between the different doses of antifibrotics (Table 3). The overall ranking of drugs by their effect on the incidence of RTIs is shown in Supplementary Table S3.

Regarding URTIs, we analyzed 5 studies with 2315 patients receiving nintedanib or pirfenidone treatment. The total number of events in this subgroup network analysis was 703. The network plot is shown in Supplementary Fig. S4. The RR of the incidence of URTIs was similar with nintedanib treatment compared to pirfenidone (RR: 0.97 CI: [0.67; 1.42]) and placebo (RR: 0.85 CI: [0.65; 1.11]). The incidence of URTI with pirfenidone therapy was also in the same range as placebo (RR: 0.87 CI: [0.67; 1.15]). In all our comparisons, the 95% CI overlapped (Supplementary Table S4/A). The overall ranking of drugs by their effect on the incidence of URTI-s is shown in Supplementary Table S4/B.

Regarding LRTIs, we analyzed 6 studies with 2736 patients receiving nintedanib or pirfenidone treatment. The total number of events in this network analysis was 278. The network plot is shown in Supplementary Fig. S5. The RR for the incidence of LRTIs for both drugs was similar to placebo (pirfenidone RR 0.94 CI: [0.66; 1.34], nintedanib RR 0.98 CI: [0.72; 1.33]) (Supplementary Table S5/A). The overall ranking of the drugs by their effect on the incidence of LRTIs is shown in Supplementary Table S5/B. No statistically significant changes in RR for incidence of URTI or LRTI were observed in placebo or antifibrotic treatment.

Confidence rating for main outcomes and subgroup analyses of network meta-analyses

Given that the outcome parameters included in our research were listed as adverse events in all studies and not as main outcomes, this resulted in a relatively high risk of bias and inconsistency, as well as high imprecision. Taking these into account, we gave a very low result in the confidence rating assessment in every analysis, including the main outcomes and the subgroup analyses as well (Supplementary Fig. S6).[43]

Publication bias

For network comparisons of currently used antifibrotics, the number of studies pooled for analysis was seven.

Pirfenidone (1800 mg)	–	0.84 [0.57; 1.23]	–	–	0.68 [0.49; 0.96]	–	–
0.84 [0.56; 1.25]	**Nintedanib (300 mg)**	–	0.77 [0.45; 1.31]	–	0.85 [0.68; 1.06]	0.65 [0.39; 1.09]	0.64 [0.38; 1.06]
0.79 [0.55; 1.16]	0.95 [0.64; 1.41]	**Pirfenidone (≈1200 mg)**	–	1.75 [0.63; 4.83]	0.87 [0.62; 1.21]	–	–
0.77 [0.45; 1.33]	0.92 [0.59; 1.45]	0.97 [0.56; 1.67]	**Nintedanib (50 mg)**	–	0.82 [0.51; 1.31]	0.85 [0.53; 1.37]	0.83 [0.52; 1.32]
0.73 [0.47; 1.12]	0.87 [0.61; 1.24]	0.91 [0.60; 1.39]	0.94 [0.56; 1.58]	**Pirfenidone (2403 mg)**	1.00 [0.75; 1.33]	–	–
0.71 [0.51; 0.99]	0.85 [0.68; 1.06]	0.89 [0.64; 1.23]	0.92 [0.59; 1.41]	0.97 [0.73; 1.29]	**Placebo**	1.04 [0.67; 1.63]	1.01 [0.65; 1.57]
0.66 [0.39; 1.12]	0.79 [0.51; 1.21]	0.83 [0.49; 1.40]	0.85 [0.53; 1.37]	0.91 [0.55; 1.49]	0.93 [0.62; 1.41]	**Nintedanib (100 mg)**	0.97 [0.62; 1.52]
0.64 [0.38; 1.08]	0.77 [0.50; 1.17]	0.80 [0.48; 1.36]	0.83 [0.52; 1.32]	0.88 [0.54; 1.45]	0.91 [0.60; 1.36]	0.97 [0.62; 1.52]	**Nintedanib (200 mg)**

The upper triangle part of the league table contains estimates based on direct comparisons, whereas the lower triangle shows estimates based on direct and indirect comparisons. RR [CI].

Table 3: **Direct and indirect comparisons of currently used antifibrotic drugs in IPF by RTI incidence and dose dependency.**

Due to the small number of included RCTs, we omit the funnel plot analysis from this manuscript.

Discussion

As there is currently no curative therapy available for the treatment of IPF, the timely diagnosis of clinically relevant treatable traits has become a primary concern.[19] RTIs are among the most common treatable respiratory events representing a big burden to patients and treatment team. In our summarized RCTs, RTIs are very often reported AEs in IPF (38.4 ± 23.5%). These events can cause serious suffering to patients with or without the trigger of an acute exacerbation.[22,24,68]

Bacterial burden in the lower respiratory tract is known to be a factor influencing IPF severity and prognosis,[69,70] as is the reduction of FVC.[71–73] Recommendations of expert panels on the comprehensive management of ILDs suggest the treatment of pulmonary traits, with RTIs being one of the most important measures.[19,73] As has been already proven in chronic obstructive pulmonary disease (COPD), early-life RTIs play a significant role in its development and progression.[74] Vaccination in chronic lung diseases is an important preventive measure, also confirmed by the 2019 coronavirus pandemic (COVID-19), as vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2) effectively reduced mortality and COVID-associated ILD by reducing the incidence of this specific RTI.[25,75,76] Vaccination against other pathogens is also extremely important in reducing infections and preventing lung damage in elderly and with underlying lung diseases (includingIPF), such as: pneumococcal vaccination regardless of age, annual influenza vaccination, ten-yearly pertussis vaccination, and RSV vaccination of people over 60 years of age.[77]

In our systematic review and meta-analysis, most treatment approaches did not change RTI incidence over the one-year period and showed comparably high rates as in placebo-treated groups. Today, either nintedanib or pirfenidone is the SOC pharmacologic treatment of choice for IPF,[73] and our meta-analysis suggests that these two drugs are safe for RTI AEs in RCTs. We did not observe any significant difference between these therapies in terms of the impact on all RTIs or on the incidence of URTI or LRTI. However, a significant RTI risk reduction was observed in one study with a dose of 300 mg/day of nintedanib[48] and similarly in another RCT of 1800 mg/day of pirfenidone,[45] emphasizing that the latter was a single-country study.

Other RCTs assessing therapies with different modes of action showed mainly similar results. Among the antibodies, we observed a significant decrease in the incidence of RTI in patients treated with simtuzumab; however, it should be noted that the study allowed for the baseline use of ACC and antifibrotic drugs, although there was no difference in their use between the two groups[51] On the other hand, a significant increase in the incidence of RTIs with romilkimab treatment was noted. In this study, more than one-third of patients received pirfenidone and ∼20% nintedanib treatment in each group.[65]

Regarding RCTs with other drugs, in a trial with interferon γ-1b treatment, we were able to confirm a significant reduction in the incidence of RTI; however, the study allowed the use of low-dose prednisolone.[62] It is important to mention that the indirect estimates made in connection with the above-mentioned drugs (simtuzumab, romilkimab, interferon γ-1b) no longer proved a significant RTI-changing effect. On the contrary, we observed a significant reduction in the incidence of RTI with everolimus; however, a serious limitation of the study is the high rate of premature discontinuation. It is important to emphasize that an acceleration of IPF progression was observed with everolimus treatment, and in this study there were lack of prespecified baseline exclusion criteria, such as disease duration, baseline respiratory function, gas exchange, 6-min walk distance, or the extent of honeycombing on chest HRCT which could be a confounding due to disease severity.[55,73,78] Across all trials analyzed, only some therapies reduced the incidence of RTIs,[55,64] though the primary endpoint was not met in these studies, and in some cases, acceleration of IPF progression was observed.[55] Highlighting the importance of rehabilitation, our analysis also included a rehabilitation RCT. The study had a small number of cases and did not significantly influence the result of the analysis.[58]

In our meta-analysis, we included RCTs regardless of predicted FVC value, and it has been proven that a decrease in FVC plays a decisive role in the prognosis of IPF.[71–73] Functionally low and high values may influence our results. The worst predicted FVC values were found in the EME-TIPAC[56] and RAINIER[51] studies (55.2 ± 10; 62.3 ± 12.2, respectively). Patients with FVC values greater than 75% in the former study were excluded. The TMP/SMX applied did not affect the incidence of RTI in that study. However, despite the fact that the authors report AE as infection-related, they mention it as a limitation in the discussion of the article that these were rather respiratory-related and not specifically infection-related events. At the same time, the study allowed the use of approved antifibrotics, so some of the patients were treated with pirfenidone.[56]

This systematic review, pairwise and network meta-analysis is the most comprehensive and up-to-date summary of different drugs intended for the treatment of IPF for the incidence of RTIs over a period of one year. We are the first to report on the RR and the safety of all pharmacological approaches for the treatment of IPF in relation to the high incidence of RTI, and we use the most up-to-date GRADE[42] and CINEMA[43] guidance, which were developed in parallel, to assess the certainty

of evidence. We included only RCTs, and our analysis comprised a large number of IPF patients and cases with a duration of at least 52 weeks to exclude seasonal changes in the incidence of RTIs.

Our results are limited by a relatively high risk of bias as the exact diagnostic methodology for our main outcome parameter was not reported. Another important limitation of the study is that the included RCTs did not publish the microbiological results of the RTIs reported in the study. Additional limitation of this analysis is that it focuses on drugs which, based on current scientific understanding, are not expected to have a direct impact in general on infection occurrence. However, it is important to acknowledge the possibility of an as-yet undiscovered correlation between these investigational drugs and a reduction in RTI incidence, because such a relationship might represent a significant breakthrough in the management of IPF and reducing the suffering of the patients. Another limitation to note is that some of the examined RCTs allowed the use of antifibrotics in the control group, and did not publish precise information on subgroups according background treatment.

According to the current ATS/ERS/JRS/ALAT Clinical Practice Guidelines, pirfenidone or nintedanib are the SOC antifibrotic drugs for patients with IPF.[73] As there is still no available therapy to improve IPF, there are several studies evaluating new substances in this deadly rare disease.[79–83] New studies will mainly use actual antifibrotics as SOC, given that these drugs have already proven their effectiveness in reducing disease progression. In the future, the introduction of add-on therapies may become the most effective treatment for this disease, and for patients and clinicians, safety is crucial in terms of incidence of this treatable trait RTI.

Our results suggest that the currently used antifibrotics are safe and do not change the incidence of RTIs without making any difference between the two drugs. Further RCTs with add-on therapies and real-world studies with RTI incidence as a main outcome might reveal the clinically most beneficial therapies to treat treatable components of IPF.

New outcome measures for clinical trials are warranted, as FVC in itself is not a good surrogate marker for clinically relevant patient-centered outcome.[84–86] In clinical trials, more emphasis should be placed on combined endpoints, including treatable traits, important for clinicians and patients, and in the future also in RTIs, as they are common and represent a burden in terms of acute exacerbation, disease progression and death.

Contributors

Z.Ma. led the conceptualization and investigation, drafting the original manuscript, with substantial contributions to writing, reviewing and editing from A.B., C.G. and C.T. Z.Ma., A.B., C.G. and C.T. accessed and verified the data. B.S. and N.G. were contributors in writing and editing, and also conducted formal analysis and visualisation. Z.Mo. and G.D. supported manuscript review and editing. C.T. was integral in conceptualization, methodology design, and project administration, while P.H. contributed to both conceptualization, reciewing and project management. G.H. provided conceptual guidance, reviewing and supervision throughout, ensuring quality control. V.M. accessed the data and contributed significantly to the conceptualization, supervision, project administration, and helped in preparing the original draft. Z.Ma and V.M were responsible for the decision to submit the manuscript.

Data sharing statement

Data are available upon reasonable request.

Declaration of interests

Z.Ma., A.B., C.G., B.S., N.G., Z.Mo., G.D., C.T., P.H. and G.H. have nothing to declare. V.M. has received consulting fees from Boehringer Ingelheim, Roche, Merck Sharp & Dohme (MSD) and Pfizer.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102966.

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