EFFICACY, SAFETY, AND TOLERABILITY OF ANTIFIBROTIC AGENTS IN RHEUMATOID ARTHRITIS-ASSOCIATED INTERSTITIAL LUNG DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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OBJECTIVE

To evaluate the efficacy, safety, and tolerability of antifibrotic agents, nintedanib and pirfenidone, in the treatment of rheumatoid arthritis-associated interstitial lung disease (RA-ILD).

METHODS

A systematic literature review was conducted following PRISMA and MOOSE guidelines. Studies assessing nintedanib or pirfenidone in RA-ILD were included. A meta-analysis was performed using a random-effects model

RESULTS

Six studies (2 randomized controlled trials and 4 observational) involving 270 RA-ILD patients met the inclusion criteria. In total, 148 received nintedanib and 122 received pirfenidone. Nearly 70% had a usual interstitial pneumonia pattern.

The pooled analysis revealed a mean FVC decline of -68.97 mL/year (95% CI: -104.85 to -32.49; p<0.001) and a mean difference of 1.15% (p=0.33; after excluding influential studies: -0.28, p=0.54). Their impact on %pDLCO has been less extensively evaluated, with a mean difference of −1.76% (p =0.36; after excluding influential studies: effect size −3.78, p<0.001). The changes in pulmonary function tests were comparable between nintedanib and pirfenidone.

Mortality rates ranged from 15% to 35%, with respiratory-specific mortality reported at 44% to 100%. Lung transplantation rates were 4–5%.

Antifibrotic therapy was associated with a pooled adverse events (AEs) rate of 73% (95% CI: 0.38–0.97; p<0.001).The most commonly reported AEs were gastrointestinal symptoms and hepatotoxicity, with higher rates in RCT (100%) compared to observational studies (25%–81.5%), likely due to stricter monitoring protocols.

Treatment discontinuation due to AEs occurred in nearly 24% of patients (95% CI: 0.16–0.40; p<0.001), being slightly higher in observational studies (30%–46%) than in RCT (23.8% in INBUILD and 24% in TRAIL1). Permanent dose reductions were common, ranging from 21.4% to 40% for nintedanib and 14% for pirfenidone.

Finally, two articles suggest that switching to pirfenidone may be a viable alternative for patients intolerant to nintedanib, although evidence is limited to 19 patients, of whom 13 (68.4%) successfully continued the second antifibrotic treatment

CONCLUSION

Antifibrotic agents demonstrated stabilization of %pFVC, with less robust evidence for %pDLCO in RA-ILD. The treatments show an acceptable safety profile and relatively low discontinuation rates. However, persistently high mortality and lung transplantation rates underscore the need for further research to determine the optimal timing for therapy initiation

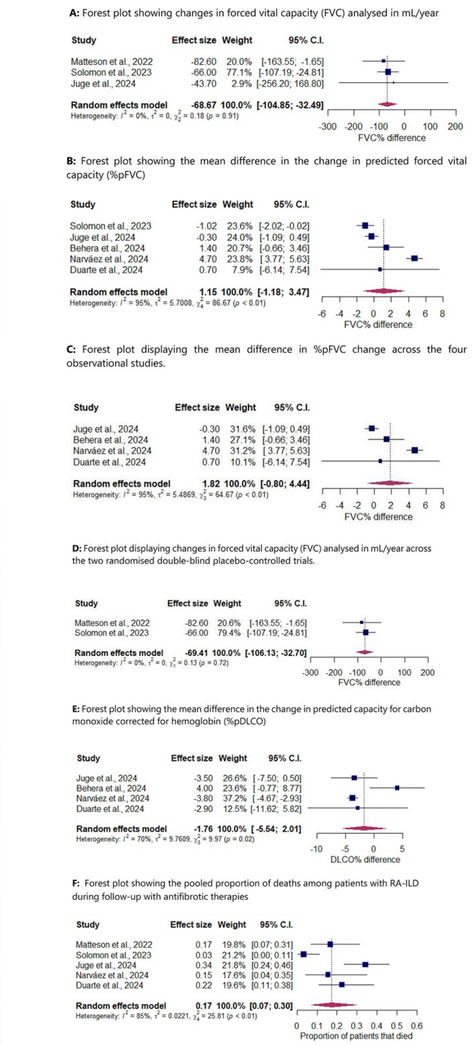

Fig. 1. Forest plots for the analysis of the impact of antifibrotic agents on rheumatoid arthritis-associated interstitial lung disease (RA-ILD).

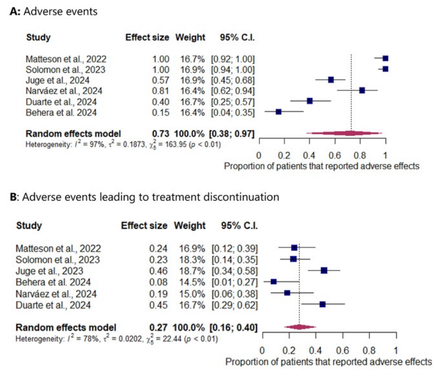

Fig. 2. Forest plots analyzing the safety of antifibrotic agents on rheumatoid arthritis-associated interstitial lung disease (RA-ILD).

Assessment of study quality—uncontrolled observational studies using the Newcastle-Ottawa scale.

Study (reference)	Intervention	Comparator	Selection	Comparability	Outcome	Total
Matteson [12]	Nintedanib	Placebo	4	2	3	9
Solomon [13]	Pirfenidona	Placebo	4	2	3	9
Juge [15]	Nintedanib and pirfenidone	No	3	0	3	6
Behera [16]	Nintedanib and pirfenidone	No	3	0	3	6
Duarte [17]	Nintedanib and pirfenidone	No	3	0	3	6
Narváez [18]	Nintedanib and pirfenidone	No	3	0	3	6

Adverse events associated with antifibrotic therapies in RA-ILD: summary of randomized controlled trials and observational studies.

	Matteson et al, 2023 N = 42	Solomon et al, 2023 N = 62	Juge et al, 2024 N = 74	Behera et al, 2024 N = 24	Narvaez et al, 2024 N = 27	Duarte et al, 2024 N = 40
Any adverse event	100 %	100 %	55 %	25 %	81.5 %	40 %
Serious adverse event[a]	61.9 %	15 %	NR	NR	0 %	NR
Adverse event leading to treatment discontinuation	23.8 %	24 %	32.4 %	0 %	18.5 %	30 %
Adverse event leading to permanent dose reduction	21.4 %	NR	NR	NR	Nintedanib 40 % Pirfenidone 14 %	NR
Discontinuation rate[b]	23.8 %	24 %	30 %	0 %	37 %	46 %
Gastrointestinal	NR	NR	40.5 %	NR	74.1 %	NR
Diarrhea	61.9 %	31 %	NR	17 %	63 %	NR
Nausea/Vomiting	21.4 %	53 %	NR	25 %	33 %	NR
Abdominal pain	11.9 %	NR	NR	NR	11 %	NR
Decreased appetite/weight loss	11.9 %	27 %	NR	17 %	37 %	NR
ALT o AST increased	14.3 %	NR	2.7 %	21 %	26 %	NR
Asthenia/Fatigue	NR	32 %	NR	NR	7.4 %	NR
Skin Rash/Photosensitivity	NR	29 %	4 %	8.3 %	0 %	NR

NR = data not reported.
[a] Adverse event that resulted in death, was life-threatening, resulted in hospitalisation or prolongation of hospitalisation, resulted in persistent or clinically significant disability or incapacity, or was deemed to be serious for any other reason.
[b] Due to adverse events or other factors, including death from ILD progression, infectious complications, or the necessity of lung transplantation.

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