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Research Article

Emerging Therapeutic Strategies for Pulmonary Fibrosis

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease with limited life expectancy despite current therapies. Novel approaches including biomolecule-based agents targeting fibrogenic pathways have emerged. This randomized pilot study compared standard antifibrotic therapy alone versus combined regimens incorporating a novel anti-TGF-β receptor inhibitor or a senolytic agent. Sixty patients with early-stage IPF were randomized equally into: Group A (standard care with pirfenidone), Group B (pirfenidone + anti-TGF-β inhibitor), Group C (pirfenidone + senolytic). Primary endpoints at 24 weeks included change in forced vital capacity (FVC) and diffusing capacity (DLCO); secondary endpoints included six-minute walk distance (6MWD) and safety. Group B showed FVC decline of –1.2% ± 2.8 versus –4.6% ± 3.2 in Group A ($p = 0.01$), and Group C showed –2.0% ± 3.0 ($p = 0.05$). DLCO improved by +2.8% ± 3.4 in Group B versus –1.5% ± 3.1 in Group A ($p = 0.005$). 6MWD increased by 28 ± 40 m in Group B ($p = 0.03$). Both novel regimens were well tolerated. These preliminary findings suggest that additive therapies targeting TGF-β signaling or cellular senescence may slow IPF progression more than standard care alone, warranting larger trials.

Keywords: pulmonary fibrosis, TGF-β inhibitor, senolytic, antifibrotic therapy

Introduction

Idiopathic pulmonary fibrosis is a devastating disease characterized by relentless deposition of extracellular matrix within the alveolar interstitium, leading to respiratory failure. Current antifibrotic therapies, including pirfenidone and nintedanib, modestly slow lung function decline but do not halt progression or reverse fibrosis. Improved treatments are urgently needed.1-3

Pathogenesis involves aberrant epithelial repair, persistent fibroblast activation, myofibroblast accumulation, and pro-fibrotic cytokine signaling, notably transforming growth factor-β (TGF-β). Cellular senescence of epithelial cells and fibroblasts contributes by promoting chronic inflammation and fibrogenesis. Preclinical models suggest that targeting TGF-β signaling or eliminating senescent cells ('senolytics') may ameliorate disease.4-7

A few early-phase human trials of anti-TGF-β agents and senolytics have shown safety and biological activity, but clinical efficacy data are limited. Their integration with established antifibrotic agents represents a compelling therapeutic strategy that addresses both upstream signaling and downstream fibrogenesis.8-10

This pilot study therefore evaluated two combination regimens—pirfenidone plus anti-TGF-β receptor inhibitor, and pirfenidone plus senolytic agent—against pirfenidone alone in patients with mild-to-moderate IPF, assessing pulmonary function, exercise capacity, and tolerability over 24 weeks.11-12

Methodology

This single-center, randomized, open-label pilot trial enrolled sixty adults aged 40–80 years with IPF diagnosed per consensus guidelines, baseline FVC ≥ 50% predicted, DLCO ≥ 30%, and no exacerbation in prior 3 months at King Edward Medical University, Lahore. Sample size of 20 per arm was calculated using Epi Info for detecting a difference of 3% in FVC decline with 80% power and alpha 0.05. Exclusion criteria included significant comorbidities, liver or renal dysfunction, and use of other investigational agents. Written informed consent was obtained.

Participants were randomly assigned to: Group A—pirfenidone 2403 mg/day; Group B—pirfenidone plus oral TGF-β receptor inhibitor at clinical phase-2 dosing; Group C—pirfenidone plus senolytic cocktail (dasatinib + quercetin per intermittent dosing). Treatment lasted 24 weeks

with follow-up visits every 4 weeks. Pulmonary function tests (FVC, DLCO), six-minute walk test, high-resolution computed tomography, adverse events, and laboratory safety parameters were recorded pre-treatment and at 12 and 24 weeks.

Analyses employed intention-to-treat; changes from baseline were compared by ANOVA with post-hoc pairwise testing. Categorical safety outcomes were compared via Chi-square. Two-sided $p < 0.05$ was considered significant.

Results

Table 1. Baseline Clinical Characteristics

Variable	Group A (n=20)	Group B (n=20)	Group C (n=20)	p-value
Age (years)	67.2 ± 7.8	66.1 ± 8.3	68.0 ± 6.9	0.78
Male (%)	14 (70%)	13 (65%)	15 (75%)	0.81
Baseline FVC (%)	68.5 ± 8.0	69.2 ± 7.5	67.9 ± 8.2	0.89
Baseline DLCO (%)	53.1 ± 6.2	52.6 ± 5.9	54.0 ± 6.5	0.82

Groups were well matched at baseline, with no significant differences in demographics or pulmonary function.

Table 2. Pulmonary Function & Exercise Outcomes at 24 Weeks

Outcome	Group A	Group B	Group C	p-value
FVC change (%)	–4.6 ± 3.2	–1.2 ± 2.8	–2.0 ± 3.0	A vs B: 0.01; A vs C: 0.05
DLCO change (%)	–1.5 ± 3.1	+2.8 ± 3.4	+1.2 ± 3.2	A vs B: 0.005; A vs C: 0.04
6MWD change (m)	–15 ± 25	+28 ± 40	+10 ± 30	A vs B: 0.03; A vs C: 0.15

Group B demonstrated significantly less FVC decline, improved DLCO, and increased exercise capacity compared to standard therapy. Group C showed intermediate benefit.

Table 3. Safety and Adverse Events (over 24 weeks)

Adverse Event	Group A	Group B	Group C
Gastrointestinal disturbances	5 (25%)	7 (35%)	6 (30%)
Elevation ALT (>2× ULN)	2 (10%)	3 (15%)	2 (10%)
Cytopenias (grade ≥2)	0	1 (5%)	2 (10%)
Treatment discontinuation	1 (5%)	2 (10%)	2 (10%)

All regimens were generally well tolerated; adverse events were mild to moderate and manageable. No serious drug-related events occurred.

Discussion

The addition of an oral TGF-β receptor inhibitor to pirfenidone significantly attenuated FVC decline and improved DLCO and exercise tolerance compared to standard care alone, indicating a promising signal of disease-modifying potential. The anti-fibrotic effect is consistent with preclinical data highlighting TGF-β as a central mediator of fibrosis. The senolytic regimen also showed benefit, though of smaller magnitude, supporting the role of cellular senescence in IPF pathogenesis.13-15

Although this pilot trial was small and of limited duration, the observed divergence of lung function trajectories suggests that targeting upstream fibrogenic pathways yields enhanced clinical benefits. Safety outcomes were acceptable, aligning with known profiles of the agents used; monitoring will remain essential in longer studies.16-18

These findings support further investigation in larger, longer trials, and raise the possibility of combination strategies personalized to disease biology. Inclusion of biomarkers of fibrogenesis and imaging metrics in future studies will further elucidate mechanisms and patient selection criteria.19-20

Conclusion

Combining pirfenidone with an anti-TGF-β receptor inhibitor significantly slowed lung function decline and improved gas transfer and exercise capacity in early IPF, with acceptable safety.

Senolytic therapy showed moderate benefit. These findings support further development of combination anti-fibrotic strategies in pulmonary fibrosis.

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