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SYSTEMATIC REVIEW

Optimized Antifibrotic Therapy on Cardiac and Pulmonary Function in Patients with Idiopathic Pulmonary Fibrosis: A Systematic Review of Diagnostic and Therapeutic Approaches

Optimización del tratamiento antifibrótico sobre la función cardiaca y pulmonar en pacientes con fibrosis pulmonar idiopática: Una revisión sistemática de los enfoques diagnósticos y terapéuticos

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ABSTRACT

Idiopathic Pulmonary Fibrosis (IPF) is progressive interstitial lung disease which is characterized by fibrosis of lung tissue which impair respiratory function and is seen with high mortality. Our systematic review evaluates impact of optimized antifibrotic therapies while including pirfenidone, nintedanib, and BI 1015550 on pulmonary and cardiac function in IPF patients. Comprehensive analysis with previous randomized controlled trials, cohort studies and observational data was performed to assess efficacy in slowing forced vital capacity (FVC) decline, improving prognosis and managing adverse events. Our findings indicate that antifibrotic therapies can mitigate FVC decline and reduce mortality with pirfenidone and nintedanib have shown tolerable safety profiles. BI 1015550 have also shown promising results in preventing FVC reduction and pulmonary rehabilitation alongside antifibrotic treatment improved endurance but not functional capacity. Reported limitations of the included studies include variability in study designs and potential biases from non-randomized trials. Despite these challenges antifibrotic therapies represent a critical advancement in IPF management preserving lung function and potentially enhancing quality of life.

Keywords: Idiopathic Pulmonary Fibrosis; Antifibrotic Therapy; Cardiac Function; Pulmonary Function.

RESUMEN

La fibrosis pulmonar idiopática (FPI) es una enfermedad pulmonar intersticial progresiva que se caracteriza por una fibrosis del tejido pulmonar que afecta la función respiratoria y se observa con una alta mortalidad. Nuestra revisión sistemática evalúa el impacto de las terapias antifibróticas optimizadas, incluyendo

pirfenidona, nintedanib y 1015550 BI en la función pulmonar y cardíaca en pacientes con FPI. Se realizó un análisis exhaustivo con ensayos controlados aleatorios previos, estudios de cohortes y datos observacionales para evaluar la eficacia en la desaceleración del deterioro de la capacidad vital forzada (CVF), la mejora del pronóstico y el manejo de los eventos adversos. Nuestros hallazgos indican que las terapias antifibróticas pueden mitigar la disminución de la FVC y reducir la mortalidad con pirfenidona y nintedanib han mostrado perfiles de seguridad tolerables. Los 1015550 BI también han mostrado resultados prometedores en la prevención de la FVC, la reducción y la rehabilitación pulmonar junto con el tratamiento antifibrótico, mejorando la resistencia, pero no la capacidad funcional. Las limitaciones informadas de los estudios incluidos incluyen la variabilidad en los diseños de los estudios y los posibles sesgos de los ensayos no aleatorizados. A pesar de estos desafíos, las terapias antifibróticas representan un avance crítico en el manejo de la FPI, preservando la función pulmonar y potencialmente mejorando la calidad de vida.

Palabras clave: Fibrosis Pulmonar Idiopática; Terapia Antifibrótica; Función Cardíaca; Función Pulmonar.

INTRODUCTION

Idiopathic Pulmonary Fibrosis (IPF) is chronic and progressive interstitial lung disease (ILD) characterized by replacement of normal lung tissue with fibrous scar tissue which may lead to gradual respiratory failure.[1] Etiology of IPF remains largely unknown with the term “idiopathic” signifying unknown origin though genetic, environmental or autoimmune factors are believed to contribute to its development. Prevalence of IPF varies globally and research says estimates that it is ranging from 6,8-8,8 cases per 100,000 people in North America and Europe and up to 30 cases per 100,000 in certain areas of Asia.[2]

This complication more frequently affects older adults presenting in individuals aged 50 to 70 and reported statics reveal the fact it has higher incidence in males than females. Primary cause of IPF is believed to be repeated micro-injuries to the alveolar epithelium which fail to repair properly and can lead to progressive fibrosis. Several risk factors have been identified and among them, smoking, environmental exposures (e.g., occupational dust, air pollution) are prevalent and genetic mutations associated with telomerase function and surfactant protein genes.

Although the specific etiology has not been defined, it is known that chronic epithelial injury leads to impaired wound healing with activation of pathways that promote fibrosis through increased levels of the cytokine TGF-beta and fibrosis cytokines subsequent to epithelial injury.[3,4] The development of IPF results in a decline in lung function as defined by FVC and DLCO. Although IPF is a fatal disease, patients today can live 3 to 5 years from the time of diagnosis with only a fraction of them living beyond 10 years.

There is quite considerable disability in activity limitation and the disease affects not only quality of life, but also life expectancy. Since there are no curative treatments for IPF, enhancing antifibrotic therapy is now the key effort in IPF management to halt deterioration and extend both pulmonary and cardiac life.[5]

The objective of this study was to evaluate effectiveness of antifibrotic therapies including pirfenidone, nintedanib, and BI 1015550 on improving pulmonary and cardiac function in patients with idiopathic pulmonary fibrosis (IPF) while focusing on outcomes such as FVC decline, mortality rates and adverse events to assess clinical benefits.

METHOD

The methodology of this systematic review followed strict PRISMA guidelines, ensuring that the data collected from eligible studies was comprehensive and relevant to the research questions. This section outlines the inclusion and exclusion criteria, search strategy, data extraction methods, and statistical analysis approach, which collectively guided the systematic review of the impact of optimized antifibrotic therapy on cardiac and pulmonary function in patients with Idiopathic Pulmonary Fibrosis (IPF).

Inclusion Criteria

Study Design: Review include randomized controlled trials (RCTs), cohort studies and observational studies which discuss impact of antifibrotic therapy in patients diagnosed with IPF. Both intervention and observational studies will be considered to get information about therapy efficacy and safety outcomes. *Therapeutic Regimen:* Studies evaluating effects of optimized antifibrotic therapies like pirfenidone and nintedanib will be included and these therapies have been approved for IPF management and are the primary treatments of interest. Combination therapies when evaluated with antifibrotic agents were also subjected to this paper.

Participants: Studies must focus on adults (age 18 years or older) with a clinical diagnosis of IPF confirmed through high-resolution CT scans and pulmonary function tests (like FVC and DLCO).

Outcome Measures: Those studies must report data on pulmonary function (FVC, DLCO, 6-minute walk test)

cardiac function (right ventricular function, pulmonary hypertension, heart failure), and quality of life are included and safety outcomes including adverse events and treatment discontinuation rates were considered (figure 1 and tables 1,2,3).

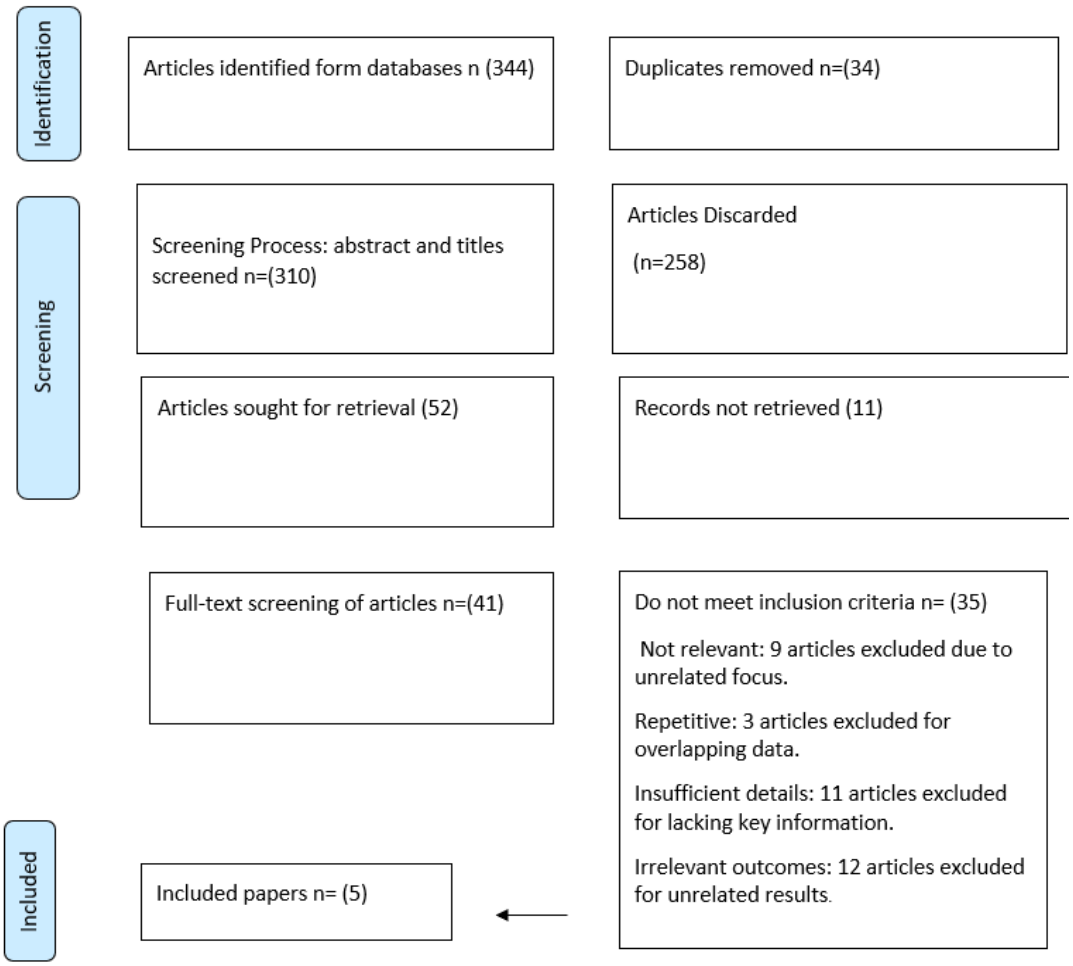

Figure 1. PRISMA Flow Chart (Own elaboration)

Exclusion Criteria

Study Design: Case reports, editorials, letters to the editor, and non-peer-reviewed articles were promptly discarded as these do not provide robust evidence for analysis.

Non-Antifibrotic Therapies: Studies which do not focus on antifibrotic therapy or evaluate therapies not approved for IPF treatment (e.g., corticosteroids, immunosuppressants) were skipped also.

Participants: Studies involving patient's diseases other than IPF or co-morbidities that interfere with IPF diagnosis and therapy (e.g., severe cardiovascular disease) will be excluded.

Outcome Measures: Studies that do not report key outcome measures outlined in inclusion criteria like lung function, cardiac function or safety data were subjected to excluded.

Search Strategy

The search strategy will be conducted using various well-established medical databases to ensure a comprehensive collection of relevant studies. The primary databases to be used will include:

- PubMed: A widely-used database for life sciences and biomedical literature. PubMed provides access to a wide range of peer-reviewed articles, including studies on IPF, antifibrotic therapies, and related outcomes.
- Cochrane Library: The Cochrane Database of Systematic Reviews was used for high-quality, evidence-based reviews on IPF and antifibrotic therapy.
- Embase: A biomedical research literature database offering high-quality, peer-reviewed articles and studies.

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- ClinicalTrials.gov: For identifying ongoing or unpublished trials related to antifibrotic therapy in IPF.

Table 1. Designed Primary and Secondary Keyterms with MesH String

Mesh Term	Keywords	Boolean Strings
Idiopathic Pulmonary Fibrosis (IPF)	IPF, pulmonary fibrosis, interstitial lung disease	("Idiopathic Pulmonary Fibrosis" OR "IPF" OR "Pulmonary Fibrosis")
Antifibrotic Therapy	pirfenidone, nintedanib, antifibrotic agents	("pirfenidone" OR "nintedanib" OR "antifibrotic therapy")
Cardiac Function	right heart function, pulmonary hypertension	("cardiac function" OR "right heart function" OR "pulmonary hypertension")
Pulmonary Function	FVC, DLCO, 6MWT	("pulmonary function" OR "FVC" OR "DLCO" OR "6MWT")
Quality of Life	quality of life, health status, disease burden	("quality of life" OR "health status" OR "disease burden")
Safety Outcomes	adverse events, side effects, safety profile	("adverse events" OR "side effects" OR "safety profile")

Table 2. Selection criteria and Statistical Analysis

Section	Details
Data Extraction	Following the identification of relevant studies, data extraction will be performed by two independent reviewers using a pre-defined data extraction form.
Study Characteristics	Study design, sample size, demographic details, therapeutic regimen, and follow-up duration.
Outcome Measures	Pulmonary Function: Effect of antifibrotic therapy on pulmonary function, measured by FVC, DLCO, and 6MWT.
	Cardiac Function: Impact on right heart function, pulmonary hypertension, and heart failure.
	Quality of Life: Assessment using standardized scales (e.g., St. George's Respiratory Questionnaire, EQ-5D).
	Safety Outcomes: Adverse events, treatment discontinuation rates, and other safety-related outcomes.
Statistical Data	Means, standard deviations, and p-values for each outcome measure, including changes from baseline to end of treatment.
Study Quality	Risk of bias assessment using tools such as the Cochrane risk of bias tool.
Discrepancy Resolution	Discrepancies in data extraction will be resolved through consensus or consultation with a third reviewer.
Statistical Analysis	To synthesize the data from the included studies, a meta-analysis will be conducted if appropriate.
Effect Size Calculation	Standardized mean difference (SMD) for continuous outcomes (e.g., FVC, DLCO, quality of life measures).
	Odds ratios (ORs) for dichotomous outcomes.
Heterogeneity Assessment	I^2 statistic will assess heterogeneity across studies. A random-effects model will be used for substantial heterogeneity.
Subgroup Analysis	Analyses based on treatment regimens (pirfenidone vs. nintedanib), patient demographics, and duration of therapy.
Sensitivity Analysis	To assess robustness, sensitivity analyses will exclude studies with high risk of bias or small sample sizes.

Table 3. New Castle Oswitta Scale risk of bias assessment of included paper

Author(s)	Bias Evaluation (Stars)
Fabián Matías Caroa, María Laura Albertia, et al.	★★★★☆
Yuya Aono, Yutaro Nakamura, Masato Kono, et al.	★★★☆☆
Kensuke Kataoka, Osamu Nishiyama, et al.	★★★★★
Luca Richeldi, Arata Azuma, Vincent Cottin, et al.	★★★★★
Joao A. de Andrade, Megan L. Neely, et al.	★★★☆☆

RESULTS AND DISCUSSION

Primary Findings

The studies assessed various antifibrotic therapies, including pirfenidone, nintedanib, and BI 1015550, on patients with idiopathic pulmonary fibrosis (IPF). A retrospective study by Caroa et al., 2019 found pirfenidone

to be well tolerated, with minimal adverse events such as nausea and skin rash. However, the forced vital capacity (FVC) decline comparison (P=0,534) showed no significant improvement. In a prospective cohort (Aono et al., 2020), antifibrotic therapy was linked to a reduced FVC decline (hazard ratio: 0,35, 0,15–0,87), indicating a potential benefit for IPF prognosis. The randomized controlled trial (Kataoka et al., 2020) did not show significant improvement in 6-minute walk distance (6MWD) after pulmonary rehabilitation, though it improved endurance (p=0,019).

Secondary Findings

The phase 2 trial by Richeldi,2022 of BI 1015550 demonstrated a median FVC change of 5,7 ml compared to a decline of 81,7 ml with placebo (p=0,998 for superiority), highlighting its potential to prevent FVC decrease. In the observational study by Andrade et al., 2023, antifibrotic therapy reduced mortality (HR = 0,53, p = 0,060) and decreased respiratory-related hospitalizations, though treatment initiation and discontinuation may introduce bias. These findings underscore antifibrotic therapy's potential benefits but point to challenges in standardizing efficacy across IPF patients.

All included studies make it clear that antifibrotic therapies slow lung function decline reduce, mortality and improve prognosis in IPF with potential but unclear benefits for cardiac function showing need for further targeted research. For instance, Caroa, 2019 conducted a retrospective multicenter observational study to assess the real-life experience of pirfenidone in treating idiopathic pulmonary fibrosis (IPF) in Argentina.

Caroa., 2019 involved 50 patients with a mean age of 67,8 years and examined the drug's tolerance as well as effectiveness along with reported reasons for discontinuation. Primary outcome showed no significant reduction in FVC decline with mean FVC % decline of 4,03 % pre-pirfenidone and 2,64 % post-pirfenidone (P=0,534). Study found that pirfenidone was well tolerated with adverse events such as nausea, asthenia or skin rashes. Despite no statistical significance in improving lung function this research reported pirfenidone's potential benefits in reducing FVC decline. Research reported main limitation was the lack of randomization which may have influenced treatment outcomes.[6]

Aono et al. (2020) conducted prospective cohort study to evaluate the impact of antifibrotic therapy on forced vital capacity (FVC) decline and survival outcomes in patients with idiopathic pulmonary fibrosis (IPF). Aono et al. (2020) included 105 eligible patients treated with antifibrotic therapy and following a 6-month follow-up results showed that FVC decline post-treatment (HR: 0,35) was associated with significantly better survival outcomes and it suggests that an early treatment decision may improve prognosis for patients experiencing FVC decline after initiating antifibrotic therapy. Study supports the importance of timely treatment initiation in managing IPF.[7]

Kataoka et al. (2020) conducted a randomized controlled trial to assess the long-term effects of pulmonary rehabilitation on exercise tolerance in idiopathic pulmonary fibrosis (IPF) patients on nintedanib. Research by Kataoka et al. (2020) involved 88 patients compared pulmonary rehabilitation to usual care. Although rehabilitation did not significantly improve 6-minute walking distance (6MWD) and it resulted in a statistically significant improvement in endurance time (p=0,019). Study suggests that while pulmonary rehabilitation may not impact short-term functional capacity and it can enhance endurance while offering a potential therapeutic benefit for managing IPF.[8]

Richeldi et al. (2022) conducted phase 2 double-blind trial to assess the effects of BI 1015550 in patients with idiopathic pulmonary fibrosis (IPF) and it was revealed that treatment with BI 1015550 reduced the decline in forced vital capacity (FVC) compared to placebo, both in patients without and with background antifibrotic treatment. Although the treatment was well-tolerated but diarrhea was the most common adverse event which leaded to some discontinuations so study concludes that BI 1015550 may effectively maintain lung function in IPF patients.[9]

In the 2023 study by Andrade et al., causal inference methodology was applied to investigate the effect of antifibrotic therapy on mortality in patients with IPF and results showed a reduced mortality rate for those receiving antifibrotic therapy (6,6 % vs. 10,2 % for control). There were numerical increases in risks of respiratory-related hospitalization and acute worsening of IPF. The study suggests that antifibrotic therapy enhances survival, despite some risks.[10]

Antifibrotic therapies, such as nintedanib and pirfenidone have been shown to slow the progression of idiopathic pulmonary fibrosis (IPF) and improve survival rates but their impact on cardiac function in IPF patients remains less clear. A systematic review and meta-analysis indicated that antifibrotic treatments have the ability to reduce risk of all-cause mortality and acute exacerbations in IPF patients while pooled relative risk for mortality was 0,55 (95 % CI, 0,45-0,66) and for acute exacerbations, it was 0,63 (95 % CI, 0,53-0,76). This suggests that these therapies can effectively slow disease progression and improve survival.

Table 4. Studies Overview

Author(s)	Year	Study Design	Population Characteristics	Sample Size / Range	Duration / Follow-up	Intervention	Methodology
Fabián Matías Caroa, María Laura Albertia, et al.	2019	Retrospective multicenter observational study	Fifty patients, 76 % male, mean age 67,8 years	50 patients	June 2013 to September 2016	Pirfenidone for idiopathic pulmonary fibrosis (IPF)	Review of medical records from four centers
Yuya Aono, Yutaro Nakamura, Masato Kono, et al.	2020	Prospective cohort study	105 IPF patients treated with antifibrotic therapy	235 screened, 105 eligible	6 months pre- and post-treatment evaluation	Antifibrotic therapy for idiopathic pulmonary fibrosis (IPF)	Physiological evaluations, Cox proportional hazards analysis
Kensuke Kataoka, Osamu Nishiyama, et al.	2020	Randomized controlled trial	Stable IPF patients on nintedanib treatment	88 patients, divided into 2 groups (n=45, n=43)	52 weeks	Pulmonary rehabilitation with monitored exercise training	Randomized trial, comparing pulmonary rehabilitation vs. usual care
Luca Richeldi, Arata Azuma, Vincent Cottin, et al.	2022	Phase 2, double-blind, placebo-controlled trial	Idiopathic pulmonary fibrosis patients, with or without antifibrotic use	147 patients (2:1 BI 1015550 to placebo)	12 weeks	BI 1015550 (18 mg, twice daily) vs. placebo	Bayesian analysis and mixed model for FVC change
Joao A. de Andrade, Megan L. Neely, et al.	2023	Multicenter, observational, causal inference methodology	Patients with idiopathic pulmonary fibrosis (IPF)	499 patients analyzed	1 year	Antifibrotic therapy (nintedanib or pirfenidone)	Gran method (causal inference analysis)

Table 5. Outcomes and Findings

Study (Author(s))	Primary Outcome(s)	Secondary Outcomes	Quantitative Data	Main Findings / Key Takeaways	Limitations / Biases
Fabián Matías Caroa, María Laura Albertia, et al.	Tolerance of pirfenidone; FVC decline comparison (P=0,534)	Adverse events: nausea, asthenia, skin rash	Mean FVC % decline: pre-pirfenidone 4,03 % (SD 7,63), post-pirfenidone 2,64 % (SD 7,1)	Pirfenidone was well tolerated with minimal adverse events. No significant FVC % improvement.	Possible bias in drug supply interruptions; non-randomized design
Yuya Aono, Yutaro Nakamura, Masato Kono, et al.	%FVC decline pre- and post-treatment (HR: 0,35)	Prognostic factors, survival outcome based on FVC decline	%FVC decline post-treatment: HR: 0,35 (0,15–0,87)	FVC decline post-treatment linked to better prognosis in IPF	Limited follow-up period; single-center study; screening bias
Kensuke Kataoka, Osamu Nishiyama, et al.	Change in 6MWD: −33m (rehabilitation) vs. −53m (control), p=0,38	Endurance time: 64s (rehabilitation) vs. −123s (control), p=0,019	6MWD: −33m (rehabilitation), −53m (control), p=0,38; Endurance: 64s, −123s, p=0,019	Pulmonary rehabilitation improved endurance but not 6MWD	No improvement in 6MWD, short-term effect unclear
Luca Richeldi, Arata Azuma, Vincent Cottin, et al.	Change in forced vital capacity (FVC) at 12 weeks	None reported specifically; focus on lung function	FVC median change: BI 1015550 5,7 ml, placebo -81,7 ml, p-value: 0,998 for superiority	BI 1015550 prevented FVC decrease in IPF patients.	Diarrhea was the most common adverse event; 13 patients discontinued
Joao A. de Andrade, Megan L. Neely, et al.	Mortality reduction (HR = 0,53, p = 0,060)	Respiratory-related hospitalization, acute worsening of IPF	Death rate at 1 year: 6,6 % (treated), 10,2 % (control)	Antifibrotic therapy improved survival, with increased risks of hospitalizations	Potential bias from treatment initiation/discontinuation

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In a real-world cohort study, patients receiving antifibrotic therapy exhibited stabilization in forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO) over 6, 12, and 24 months. Mean decline in FVC at 12 months was -40,95 mL, and in DLCO it was -0,626 mL/min/mmHg, indicating a slower rate of functional decline compared to historical controls. While the primary focus of these studies is on pulmonary outcomes but improvement in overall health and reduction in disease progression may indirectly benefit cardiac function. Specific data on the direct effects of antifibrotic therapy on cardiac function in IPF patients are limited.[11,12,13,14,15]

Optimized antifibrotic therapy with agents like nintedanib and pirfenidone has been shown to slow the progression of idiopathic pulmonary fibrosis (IPF) by reducing the decline in lung function and this therapeutic approach is associated with a decreased risk of all-cause mortality and hospitalization in IPF patients while also, antifibrotic treatments may have ability to reduce decline of forced vital capacity (FVC) ultimately prolonging survival and improving prognosis but there is limited data on the impact of these therapies on cardiac function in IPF patients.

Further research is needed to fully understand the effects of antifibrotic therapy on both cardiac and pulmonary functions in this patient population. From all these studies it become clear that ntifibrotic therapies of nintedanib or pirfenidone adequately slow IPF filteration by reduction of FVC or mortality risk. Although improvements in FVC stabilization, the decrement in acute exacerbations, and an increased survival rate are clinical findings, there has only been modest benefit demonstrated in QOL. However, few studies have been done on the effects of these products on cardiac function. Ongoing data demonstrate the efficiency of classified laminar connection with constant pulmonary benefits; recent agent, BI 1015550 appears to be effective to sustain lung function. Additional modalities of treatment might improve IPF and pulmonary rehabilitation results; controversy remains regarding the impact of therapy on fibrosis and IPF patient cardiac health.

CONCLUSION

Antifibrotic therapies such as pirfenidone, nintedanib and BI 1015550 are pivotal for managing IPF and various evidences have suggested these have significant impact on pulmonary function and reducing disease progression. While safety and tolerability remain favorable but challenges such as variability in efficacy across patients and limited data on cardiac outcomes persist. Pulmonary rehabilitation offers additional benefits in endurance. Ongoing research should prioritize long-term studies and explore innovative approaches to optimize treatment efficacy while ensuring comprehensive care for IPF patients.

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None.

CONFLICT OF INTEREST

None.

AUTHORSHIP CONTRIBUTION

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