Treatment Discontinuation in Idiopathic Pulmonary Fibrosis: A Systematic Review of Antifibrotic Drug Use and Tolerability

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INTRODUCTION

- Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease of unknown origin, typically leading to respiratory failure and death within 2–5 years of diagnosis[1]
- IPF predominantly affects middle-aged and older adults and often presents with non-specific symptoms such as exertional dyspnea, persistent dry cough, and inspiratory crackles[2]
- Disease progression is driven by abnormal lung repair, resulting in fibrotic scarring, tissue stiffness, and impaired gas exchange, as reflected in altered pulmonary function tests[2]
- Antifibrotic agents, including nintedanib and pirfenidone, have transformed the treatment of IPF, which was previously limited to supportive care and lung transplantation[2]
- The chronic, progressive nature of IPF necessitates prolonged treatment; however, treatment discontinuation remains a significant challenge in clinical practice[1]

OBJECTIVES

- This systematic review aimed to assess the rates of and reasons for treatment discontinuation in patients with IPF

METHODS

- A systematic literature search was conducted on May 14, 2025 in the Embase® and MEDLINE® databases and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, to identify articles that reported data on rates and reasons for discontinuation of treatment in patients with IPF
- The search strategy employed relevant keywords to identify English-language studies focusing on the rates of and reasons for treatment discontinuation in patients with IPF
- Inclusion criteria were pre-defined, with a specific emphasis on the full-text articles reporting discontinuation data (see Table 1). Two independent reviewers initially screened the titles and abstracts of all records identified through the electronic search. Subsequently, the same reviewers assessed potentially relevant full-text articles
- In cases of disagreement or uncertainty regarding inclusion, a third independent reviewer was consulted to achieve consensus

Table 1: Inclusion criteria

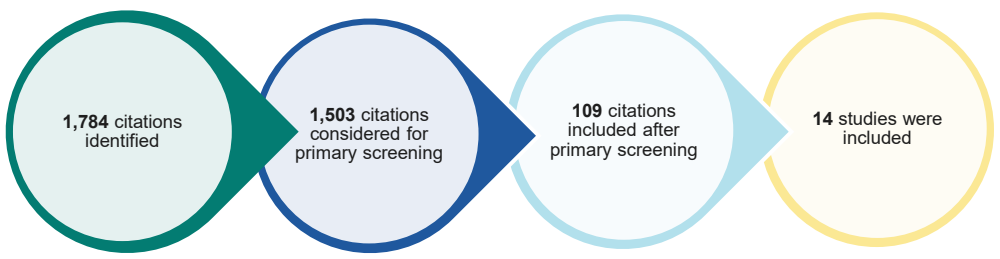
Population	▪ Patients diagnosed with IPF
Intervention and comparator	▪ No restriction
Outcomes	▪ Rate of discontinuation of antifibrotic drugs ▪ Reason for discontinuation of antifibrotic drugs
Study design	▪ Observational studies ▪ Prospective observational ▪ Retrospective observational ▪ Cohort studies ▪ Case-control studies ▪ Real-world evidence studies
Publication type	▪ Full-text articles
Language	▪ English
Time frame	▪ Inception–present (2025)
Country	▪ No restriction

Key: IPF, idiopathic pulmonary fibrosis.
Note: No restriction was applied for the age of the patients with IPF.

RESULTS

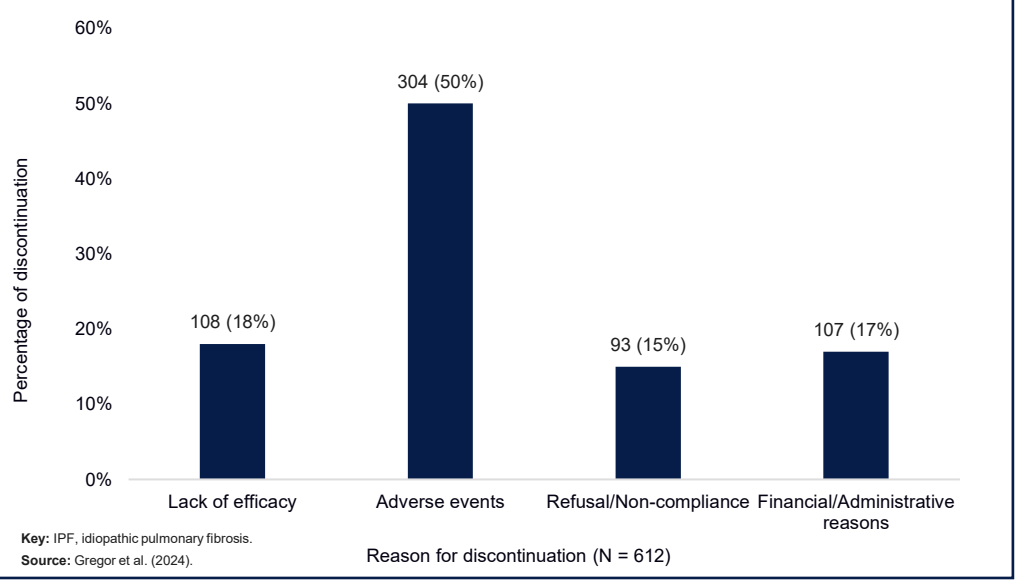
- A total of 1,784 citations were identified, of which 281 were conference abstracts and were excluded from screening. The remaining 1,503 citations underwent primary screening, resulting in 109 articles eligible for full-text review. After secondary screening, 14 studies were included. The study flow diagram is provided in Figure 1

Figure 1: Study flow diagram



- The majority of the included studies were observational in design, comprising nine retrospective and five prospective studies. More than half (n = 8) were conducted in Europe (France: 3; multi-country: 2; Germany, Spain, and England: 1 each)[3-10], followed by Japan (n = 3)[1, 11, 12], Korea (n = 2)[13, 14], and the United States (n = 1)[2]
- Pirfenidone and nintedanib were the most commonly studied antifibrotic therapies. Five studies assessed pirfenidone alone[7, 9, 11-13], six assessed pirfenidone and nintedanib[1-4, 6, 8], and three assessed nintedanib alone[5, 10, 14]
- The sample size of included studies varied from 30[11] to 1,313[6] patients
- Discontinuation was mainly due to adverse events (AEs; 50%), followed by lack of efficacy (18%), refusal/non-compliance (15%), and financial/administrative reasons (17%) (Figure 2)[4]
- Common AEs leading to discontinuation of pirfenidone included anorexia (11%), rash (11%), and gastrointestinal issues (10%); common AEs leading to discontinuation of nintedanib included anorexia (3%), nausea (2%), and weight loss (2%)[8]

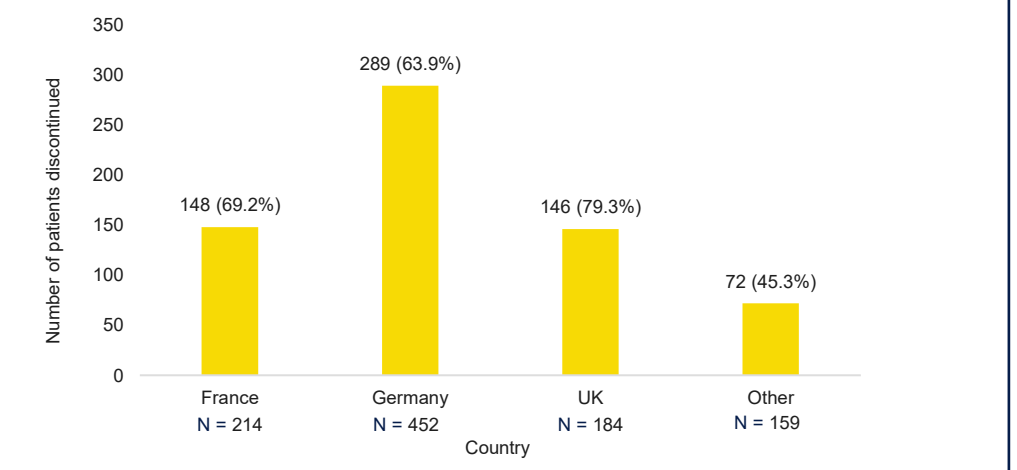
Figure 2: Reasons for treatment discontinuation in IPF



Key: IPF, idiopathic pulmonary fibrosis.
Source: Gregor et al. (2024).

- In a Spanish study, discontinuation was higher for nintedanib (64%) than pirfenidone (54.4%)[3]
- A French study reported that 51.5% of patients receiving pirfenidone discontinued within 12 months (mean time to discontinuation [standard deviation]: 126.4 [91.4] days), whereas nintedanib was discontinued within 12 months in 43.8% of patients (mean time to discontinuation [standard deviation]: 142.5 [95.7] days)[6]
- A European registry (n = 1,009) reported median (interquartile range) time to pirfenidone discontinuation as 249.0 (90.0–461.0) days in France, 176.0 (60.0–401.0) in Germany, and 201.5 (88.0–398.0) in the UK, which had the highest early discontinuation rate (79.3%) (Figure 3)[9]
- In this European registry, patients who discontinued early were predominantly male (80%) and current/ex-smokers (62.5%), with a mean age of 69.6 years and a mean disease duration of 1.7 years at the time of diagnosis[9]
- In Japan, discontinuation rates were higher among elderly (≥ 75 years) than younger (< 75 years) patients (65% vs 36%; p = 0.007)[12]
- A study conducted in South Korea reported that the rate of nintedanib discontinuation due to AEs was significantly higher in patients with advanced IPF than in patients with non-advanced IPF (68.0% vs 40.0%, p = 0.004)[14]

Figure 3: Early discontinuation (within 2 years) rate of antifibrotic drug by country



Key: UK, United Kingdom.
Source: Cottin et al. 2018.

CONCLUSIONS

- Treatment discontinuation in IPF is frequent, with AEs being the leading cause. Discontinuation rates vary notably by region, age group, disease severity, and antifibrotic therapy (pirfenidone vs nintedanib)
- Early discontinuation remains a major challenge, limiting the long-term benefits of therapy. Improved management of side effects, patient support, and tailored treatment strategies is essential to enhance adherence and optimize outcomes in IPF

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