# Investigation into the tolerability of two antifibrotic drugs in the treatment of Idiopathic Pulmonary Fibrosis

Kate Biddle[1], Roselyn Rose'Meyer[1].
[1]School of Pharmacy and Medical Sciences, Griffith University, Gold Coast Campus, Queensland, Australia, 4222.

## INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a terminal respiratory condition that causes the progressive scarring of lung tissue. There are no curative therapies for IPF however nintedanib and pirfenidone have been shown to slow disease progression. Despite their efficacy, they are known to cause significant side effects that limit treatment continuation. This study included a scoping review to define antifibrotic tolerability and an audit of local data to assess antifibrotic tolerability in patients from a metropolitan hospital.

## METHODS

A scoping review following the PRISMA-ScR guidelines was conducted to outline a definition of drug tolerability and the variables used to assess antifibrotic tolerability. Data from a hospital's IPF database (n=37) was reviewed and compared to trends found in similar published international studies. [1,2,3]

## RESULTS

A literature search identified 1,504 relevant articles; however 28 studies were included in the final scoping review. From these original articles, only three studies clearly outlined how they defined and evaluated antifibrotic tolerability. The key variables used to determine tolerability were: medication discontinuation rate, description and incidence of side effects, and time until drug cessation. Treatment discontinuation for nintedanib and pirfenidone were similar between the local data (33%, 58%) and a comparator study (31%, 71%) that investigated both antifibrotics.

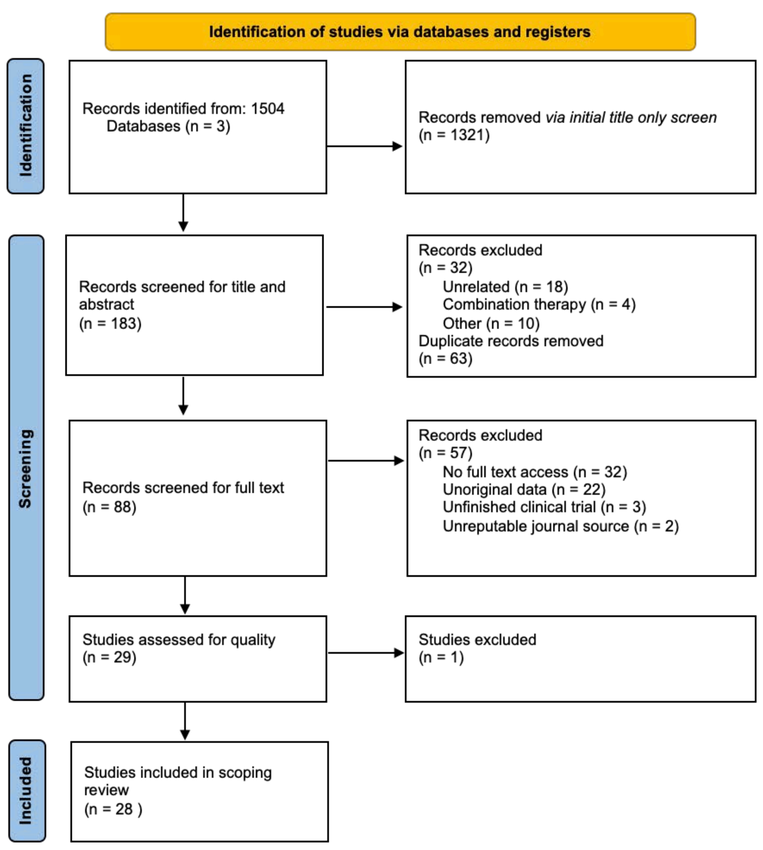


**Figure 1.** Adapted PRISMA diagram depicting flow of information

| Articles | Definition of tolerability | Clarity of definition | Tolerability outcome |
|---|---|---|---|
| (Crestani et al., 2019) | Tolerability was based on the recording and reporting of ADE for the duration of the trial and 28 days after treatment if discontinued | N/A: did not claim to investigate tolerability as the focus was on safety signals | Drug was tolerable and no new safety signals identified. Diarrhoea was the most common ADE |
| (Fletcher et al., 2018) | Tolerability was likely based on treatment discontinuation due to ADE | Unclear | Drug was generally well tolerated however discontinuation rates were higher than those reported in clinical trials |
| (Hirasawa et al., 2020) | Tolerability was likely based on drug persistent rate and evaluated if a dose reduction or antidiarrheal therapy related to drug persistance | Partially clear | Serum albumin was the only characteristic associated with a higher incidence of discontinuation.<br>Antidiarrheal therapy prolongs the tolerable duration of treatment |
| (Kato et al., 2021) | Tolerability was likely based on continuation of drug at 12 mths of treatment | Partially clear | Poor performance status at treatment initiation was a significant risk factor for treatment discontinuation after 12 months |
| (Komatsu et al., 2022) | Tolerability was determined by the incidence of ADE causing dose reduction, discontiniation and reasons for treatment cessation | Partially clear | Similar continuation rates between elderly and non elderly |
| (Liang et al., 2021) | Investigation of adverse events, dose reduction and discontinuation | Clear: Tolerability was well evaluated by recording and discussing ADE, dose reduction and discontinuation | Diarrhoea was the most common adverse event and hepatic insufficiency was commonly associated with reduction or discontinuation |
| (Nakamura et al., 2019) | Tolerability was evaluated based on incidence of permanent or temporary discontinuation due to ADE | Clear: Tolerability was based on incidence of permanent or tempoary dicosntinuation due to ADE | Drug was tolerable for patients with severe disease that were not fit for clinical trials and diarrhoea was the most common ADE |
| (Raman et al., 2022) | Adverse effects including 12 month mortality, side effects and compliance data was used to ascertain overall tolerability and safety | Clear: ADE, 12 month mortality, side effects, compliance data were collected to ascertain overall tolerability | Nintedanib appeared to be well tolerated and did not have deliterious effects when taken with other immunosupressive drugs. |
| (Richeldi et al., 2014) | Tolerability was considered synonymous with safety in this RCT | N/A: did not specifically investigate tolerability, focus on discontinuation rates | Discontinuation occurred in 5% of patients with diarrhoea as the most common ADE. Despite this the dosing regime was successful in minimising discontinuation as dose intensity was >90% |
| (Takeda et al., 2020) | Tolerability was likely based on incidence of ADE and discontinuation rates | Unclear | Tolerability was similar between young and elderly patients |
| (Toi et al; 2019) | Investigated medication discontinuation with no mention of tolerability. However discontinuation is commonly used to evaluate tolerability in similar studies | N/A: did not specifically investigate tolerability, focus on discontinuation rates | Patients who required dose reductions were significantly older and body surface area was significantly lower in the patient group who required a reduction or discontinued treatment |
| (Uchida et al., 2021) | Unclear, tolerability was likely based on incidence of ADE and drug discontinuation | Unclear | Elderly patients had a higher incidence of discontinuation, anorexia and nausea. In addition treatment discontinuation was frequent in patients with low BMI and FVC |

**Table 1.** Definition of tolerability and study outcomes in articles investigating nintedanib treatment.

| Article | Definition of tolerability | Clarity of definition | Tolerability outcome |
|---|---|---|---|
| (Chaudhuri et al., 2014) | Tolerability was based on adherence and compliance | Unclear | Pirfenidone was well tolerated especially with expert review and interventions to minimise impact of ADE.<br>All discontinuations occurred in the first 8 weeks |
| (Cottin et al., 2018) | Tolerability was likely based on adverse events and drug persistence | Unclear | Dose reduction had a favourable outcome on treatment persistence whilst age, female gender and prior steroid use were factors for early discontinuation |
| (Dhooria et al., 2020) | Tolerability was likely based on the description of dosing and discontinuation of treatment due to ADE | Partially clear | Pirfenidone was not well tolerated at full dose in the majority of patients and BMI was the only predictor of discontinuation due to ADE |
| (Fang et al., 2020) | The study evaluated 'safety' in terms of ADE, dose adjustments, discontinuation and time to discontinuation | Unclear | Pirfenidone was well tolerated in most lung fibrosis patients except for those with IPF, however the majority of patients still had sufficient tolerance |
| (Khanna et al., 2016) | Tolerability was likely assessed by the frequency and type of treatment emergent ADE and discontinuation rates | Unclear/inferred: frequency and type of TEAE reflect favourable tolerability and discontinuation | Pirfenidone had an acceptable tolerability profile however longer titration was associated with improved tolerability |
| (King et al., 2014) | Tolerability was not investigated in this study however treatment discontinuation was evaluated | N/A: tolerability not specifically investigated | Treatment was associated with an acceptable side effect profile |
| (Konishi et al., 2015) | Tolerability was based on the CPI assessment where 51 was the cut off | Partially clear | Pirfenidone was better tolerated in patients with milder disease symptoms |
| (Miedema et al., 2022) | Limited differentiation between safety and tolerability but it was likely based on a descriptive analysis of ADE | Unclear | The drug has an acceptable safety and tolerability profile in asbestosis however dose reductions were required due to GIT discomfort, rash and dizziness. |
| (Sakayori et al., 2019) | Tolerability was based on the causes of discontinuation, adverse drug reactions and rate of discontinuation at 6mths and 1yr | Partially clear | A difference in tolerability between elderly and younger patients was detected as older patients had higher rates of GIT side effects and treatment discontinuation |

**Table 2.** Definition of tolerability and study outcomes in articles investigating pirfenidone treatment.

| Article | Definition of tolerability | Clarity of definition | Tolerability outcome |
|---|---|---|---|
| (Barratt et al., 2018) | Tolerability was based on treatment discontinuation and reasons for cessation of therapy | Unclear | ADE for both medication were comparable to previous real world trials, no independent varaiables were identified to predict discontinuation |
| (Cilli et al., 2021) | Tolerability was based on the type of ADE and discontinuation of 1st and 2nd line antifibrotic | Unclear | Switching antifibrotics may be a feasible option for patients who do not tolerate the first line option. |
| (Galli et al., 2017) | Tolerability was based on drug discontinuation as a result of ADE | Unclear | Drug ADE profiles and tolerability were similar to those seen in clinical trials despite including patients with worse baseline characteristic |
| (Hughes et al., 2016) | Tolerability was likely based on the development of ADE and subsequent dose interruptions | Unclear | Discontinuation rates were similar to those observed in clinical trials and side effects can be managed effectively using supportive therapy |
| (Oishi et al., 2019) | Tolerability appeared to be synonymous with the investigation of discontinuation rates, persistence rates and predictive factors for discontinuation | Unclear | Poor performance status and delay in treatment initiation were associated with treatment discontinuation |
| (Takehara et al., 2022) | Discontinuation rates were considered to determine tolerability of the medication | Unclear | No significant difference between discontinuation rates of nintedanib and pirfenidone, both medications suggested to have similar tolerability |
| (Wright et al., 2021) | Tolerability likely based on discontinuation and incidence of ADE | Partially clear | Both demonstrated to have acceptable safety profiles however nintednaib was 'better' tolerated which could influence survival |

**Table 3.** Definition of tolerability and study outcomes in articles investigating both nintedanib and pirfenidone treatment.

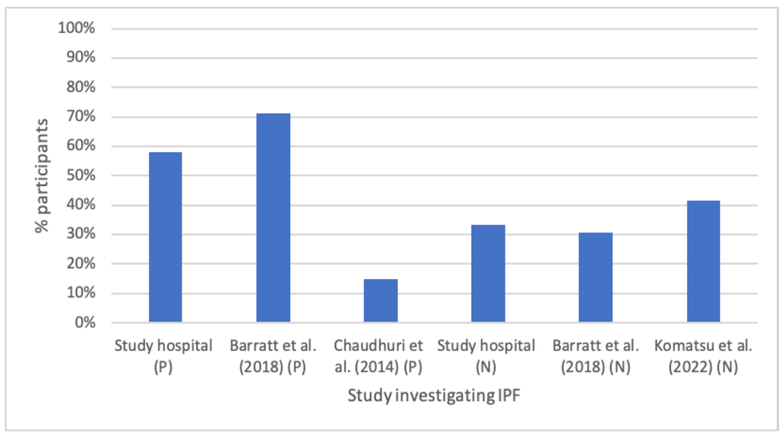


**Figure 2.** Percentage of participants who discontinued treatment from the study hospital (n=19 for pirfenidone, n=18 for nintedanib) and comparator studies by Barratt et al. (2018) (n=115 for pirfenidone, n=49 for nintedanib group), Chaudhuri et al. (2014) (n=40) and Komatsu et al. (2022) (n=65) P; pirfenidone treatment, N; nintedanib treatment.

## DISCUSSION

This scoping review found that medication tolerability is an ambiguous term that is poorly defined in the literature investigating nintedanib and pirfenidone treatment.

The review identified that an assessment of tolerability is often made based on the discussion of side effects, dose reductions, treatment discontinuation rates, the incidence of treatment interruptions, 12-month mortality, and medication compliance. Factors that were identified to be important when assessing drug tolerability and outcome included patient age, gender, disease severity, the type of side effects experienced and commencement of supportive therapies. Following the scoping review, it is suggested that tolerability is defined as the capacity of a patient to continue taking the antifibrotic medications at an effective dose despite experiencing side effects of any severity. In addition, the review highlighted a gap in the literature regarding the influence of concurrent medications and comorbidities on antifibrotic tolerability. This presents as an opportunity for further research.

The audit of local data was found to be consistent with discontinuation rates in the published literature. A common theme identified across the published studies was that patients with characteristics that are associated with poor tolerability, may benefit from earlier reviews, as discontinuation rates were highest in the first few months of treatment. Therefore, the addition of supportive interventions earlier in therapy may increase the likelihood of long term antifibrotic tolerability.

## REFERENCES

1. Barratt, S. L., Mulholland, S., Al Jbour, K., Steer, H., Gutsche, M., Foley, N., Srivastava, R., Sharp, C., & Adamali, H. I. (2018). South-West of England's Experience of the Safety and Tolerability Pirfenidone and Nintedanib for the Treatment of Idiopathic Pulmonary Fibrosis (IPF). *Front Pharmacol*, *9*, 1480. https://doi.org/10.3389/fphar.2018.01480
2. Chaudhuri, N., Duck, A., Frank, R., Holme, J., & Leonard, C. (2014). Real world experiences: Pirfenidone is well tolerated in patients with idiopathic pulmonary fibrosis. *Respiratory Medicine*, *108*(1), 224-226. https://doi.org/10.1016/j.rmed.2013.11.005
3. Komatsu, M., Yamamoto, H., Ichiyama, T., Kawakami, S., Uehara, T., Yoshikawa, Y., Kitaguchi, Y., Ushiki, A., Yasuo, M., & Hanaoka, M. (2022). Tolerability of nintedanib in the elderly with idiopathic pulmonary fibrosis: A single-center retrospective study [Article]. *PLoS ONE*, *17*(2 February). https://doi.org/10.1371/journal.pone.0262795

HREC/2023/QGC/92773

Scan here to contact me & find out more