Journal of Pulmonary Medicine

Review Article

A SCITECHNOL JOURNAL

Antifibrotic Agents for Non-Idiopathic Lung Fibrosis: A Systematic Review

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Abstract

Nintedanib and Pirfenidone are the only two medications approved for the treatment of idiopathic lung fibrosis. Both medications can decrease the decline in FVC (forced vital capacity). With the advances in imaging techniques, particularly computed tomography, other types of fibrotic pulmonary diseases are currently identified. These types are known as non-idiopathic pulmonary fibrosis (non-IPF).

Most of non-IPF pathological and clinical manifestations resemble those of IPF. Hence, anti-fibrotic agents used for the treatment of IPF could still be used for the treatment of non-IPF. However, the safety and efficacy of Nintedanib and Pirfenidone for this new indication is still unclear. Therefore, the aim of this systematic review is to examine the medical literature to evaluate the use of anti-fibrotic agents in the treatment of non-IPF disease.

The literature was reviewed through Medline, PubMed, Google scholar, and Ovid database in the duration between 2010 and 2020. Searching terms included were a combination of ''Anti-fibrotic agents'' AND'' non-idiopathic lung fibrosis''. Following this, results were filtered to include only original research articles investigating the management of non-IPF using anti-fibrotic agents. Selected trials mentioned the type of anti-fibrotic agent. Eight articles were found eligible to be included in this systematic review. Current data on the treatment of non-idiopathic pulmonary fibrosis is scarce. Further studies are required to confirm the safety and tolerability of anti-fibrotic agents for this particular indication.

Keywords: Anti-Fibrotic; Treatment; Non-Idiopathic lung fibrosis; Efficacy; Safety

Introduction

Anti-fibrotic agents are considered a disease modifying pharmacological class that was initially used for the treatment of idiopathic pulmonary fibrosis [1]. The prototype of this class is Pirfenidone [2]. The discovery of this class was initially from in vitro research [2]. Pirfenidone showed a significant reduction in the process of pulmonary fibrosis in some experimental models [3].

More studies started to investigate Pirfenidone use for the treatment of idiopathic pulmonary fibrosis, both in vivo and in vitro [4]. Pirfenidone was successful in reducing the morphological, as well as biochemical manifestations of the disease [5]. It also reduced the rate of proliferation of pulmonary fibroblasts, in addition to collagen synthesis [6]. Hence, anti-fibrotic agents became a proposed option for the treatment of idiopathic pulmonary fibrosis [7].

Following the success of Pirfenidone, other agents were developed [8]. However, only nintedanib, in addition to Pirfenidone, showed high levels of safety and efficacy in the treatment of idiopathic pulmonary fibrosis [9]. Therefore, they are the only recommended agents by the most recent guidelines globally [10].

Yet, with recent advances in diagnostic techniques, a new category of pulmonary fibrosis has been detected, which is known by non-idiopathic pulmonary fibrosis [11]. Patients with this newly identified subset of pulmonary fibrosis usually have similar clinical manifestations to patients with idiopathic pulmonary fibrosis [12]. However, they showed to be poor responders to immunosuppressant, in contrast to idiopathic pulmonary fibrosis patients. Also, they have a poor prognosis [13].

Because of the similarity in pathological features of idiopathic and non-idiopathic pulmonary fibrosis, research has been directed to exploring the role of anti-fibrotic agents in the treatment of non-idiopathic lung fibrosis [13].

Though it is still unclear if the use of nintedanib and pirfenidone is effective and safe for the indication of treating non-idiopathic pulmonary fibrosis [14]. This is mainly attributed to the rarity of the disease and the scarcity of articles investigating the use of anti-fibrotic agents in the treatment of non-idiopathic pulmonary fibrosis [15].

Therefore, this systematic review aims to examine the literature for the role of the anti-fibrotic agent in the management of non-idiopathic pulmonary fibrosis patients.

Review

Methodology

This systematic review of the literature was carried out in compliance with the PRISMA checklist recommendations for systematic review and meta-analysis. This systematic review was performed through searching electronic databases to include eligible articles till January 2020 in

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Received Date: 17 January, 2022; **Accepted Date:** 31 January, 2022; **Published Date:** 07 February, 2022

four databases, including Medline, Ovid, Google Scholar, and PubMed.

Search strategy

Searching terms included ''Anti-fibrotic agents" AND ''non-idiopathic pulmonary fibrosis". All the titles, as well as abstracts that appeared from this search, were reviewed thoroughly to prevent missing any eligible articles. The results were then refined to include only original research articles investigating the role of anti-fibrotic agents in the treatment of non-idiopathic pulmonary fibrosis. Moreover, the selected trials mentioned the type of anti-fibrotic agent and whether the safety or efficacy of the medication is evaluated. Additionally, all study designs from different countries were included. Only trials that are published in the English language were classified as related articles, which can be further evaluated in the second step.

Eligibility criteria

After this stage, the inclusion criteria to select the studies that will be considered in the systematic review were determined. Abstracts were examined manually to choose the appropriate abstracts to be considered. The inclusion criteria were mentioning enough data on the anti-fibrotic agent used. Moreover, only trials recruiting adult participants were included. Furthermore, references of selected trials were evaluated to identify any related articles. Finally, the required data sets were gathered from the final record of eligible articles and summarized. Articles were excluded in case of in vitro or animal involvement, overlapped or incomplete data, and unavailability of full text articles or inappropriate study design. Full details on the search strategy are shown in Figure 1.

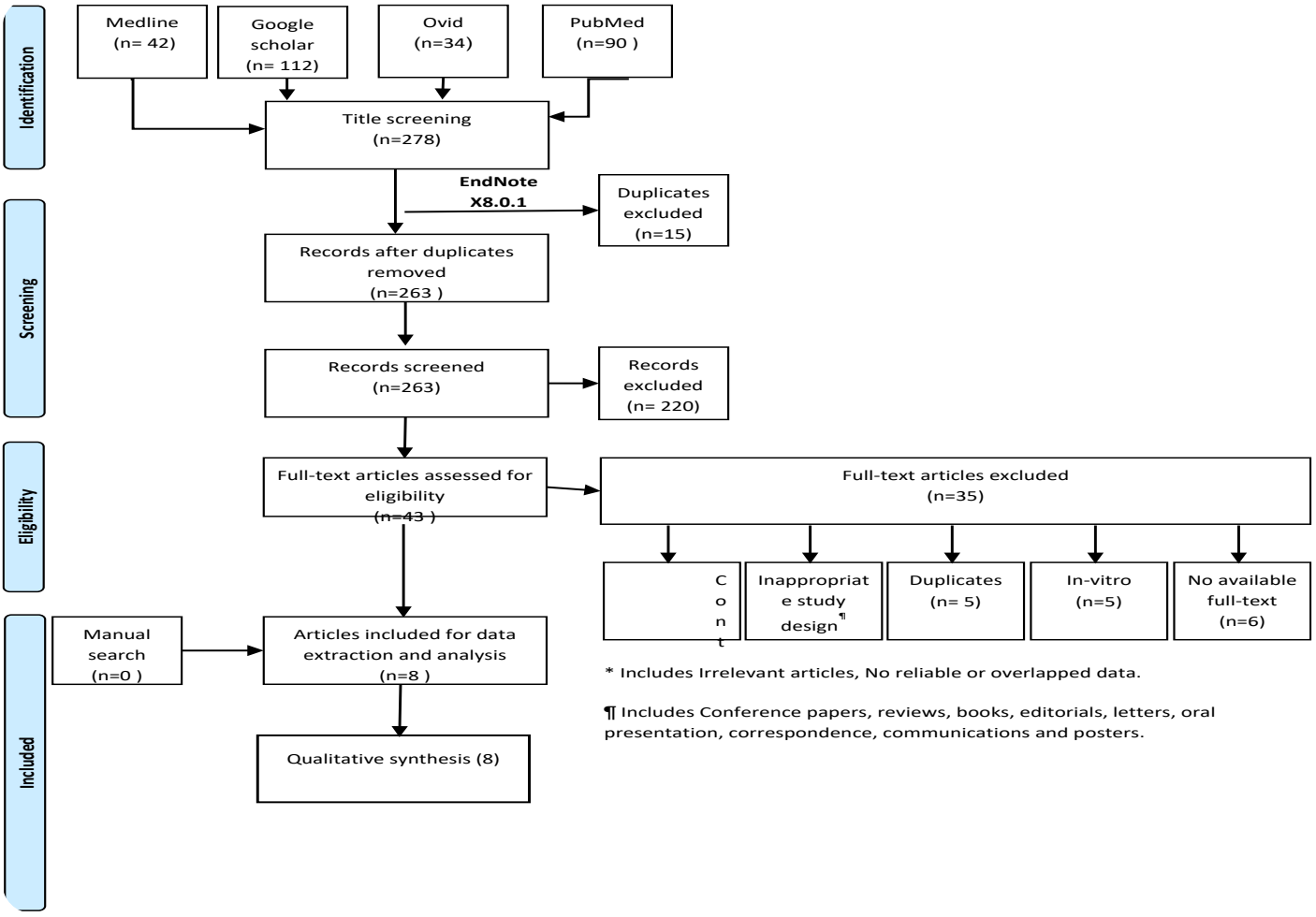

Figure 1: Description of search strategy

Data review and analysis

The first step included a preliminary review, a specially designed excel sheet was used for data extraction. Selected data from eligible studies were then revised through the excel sheet. Any articles that were published by one research group that investigate similar variables were reviewed for any possible duplication. Cochrane, a quality assessment tool, was also used to evaluate the quality of the included clinical studies. Data were then statistically described in terms of frequencies (number of cases) and valid percentages for categorical variables. Mean, standard deviations, Medians, and interquartile ratios were used to describe the numerical variable. All statistical calculations were performed by IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 26 for Microsoft Windows.

Before conducting any study related procedures, institutional approval

was obtained. There was no need to get consent form as the study is not involving any interventions on patients.

Results

After searching the abstracts and checking for the eligibility criteria in identified potential abstracts, a total of eight articles were considered as eligible to be included in the present systematic review that was published between 2010 and 2020, covering a total of 1832 patients who had non-idiopathic pulmonary fibrosis.

Out of the eight studies, three studies had a randomized, blinded controlled design, while only one study had an observational cohort design. Additionally, four studies had a retrospective design [16-23].

Furthermore, two studies evaluated the use of nintedanib, while three studies evaluated the use of Pirfenidone, and three studies included patients taking either nintedanib or pirfenidone [16-23].

According to extracted results, all the trials considered the evaluation of the safety and\or efficacy of either pirfenidone or nintedanib or both in the management of non-idiopathic pulmonary fibrosis. The included trials are discussed in detail in Table 1.

Author	Year of study	Study design	Sample size	Type of antifibrotic agent	objective	outcome
Llanos et al. [17]	2019	A multicenter-retrospective study	34	Pirfenidone and Nintedanib	To evaluate the effect of both medications in progressive non-idiopathic pulmonary fibrosis	After a follow up of one year, forced vital capacity (FVC) was reduced in three patients, between 5 to 10%. Other patients were either stable or improving. The most common adverse events reported were: 20% hyper transaminasemia, 15% weight loss, and 27% diarrhea. Only five patients could not tolerate the treatment and stopped it
Flaherty et al. [18]	2019	Randomized double-blind, placebo-controlled, phase 3 trial	663	Nintedanib	To examine the efficacy and safety of nintedanib in progressive non- idiopathic pulmonary fibrosis	The drug was effective in controlling non-idiopathic pulmonary fibrosis.
Torrisi et al. [19]	2019	Retrospective analysis	11	pirfenidone (10 patients) and nintedanib (1 patient)	To investigate the role of antifibrotic agents in progressive non-IPF interstitial lung diseases	Median FVC after a six month follow up was 46.5%. Both drugs were well tolerated, but a dose reduction was needed in 2 patients due to rash and nausea. Three patients were intolerant to the treatment. Antifibrotic treatment may be a promising treatment in progressive non- IPF if no other options are available.

Distler et al. [20]	2019	a randomized, double-blind, placebo-controlled trial	576	Nintedanibv	To investigate the efficacy and safety of nintedanib in patients with ILD with systemic sclerosis.	The decline in FVC\year was lower with nintedanib; no other clinical benefits of nintedanib was shown for systemic sclerosis. The adverse events of nintedanib observed were similar to those observed in idiopathic pulmonary fibrosis; other adverse effects were mainly gastrointestinal, including diarrhea, which was the most common adverse event, reported in 75.7% of patients.
Matsumura et al. [21]	2018	retrospective study	31	Pirfenidone	To determine if pirfenidone can improve the outcomes of acute exacerbations in non-IPF	The survival rate in the pirfenidone patients was not significantly different from non- pirfenidone patients at 30 and 90 days. Pirfenidone may decrease the inflammation in acute exacerbation of non-IPF patients.
Behr et al. [22]	2017	a randomized, double-blind,	11	pirfenidone (10 patients) and nintedanib (1 patient)	To investigate the role of antifibrotic agents in progressive non-IPF interstitial lung diseases	Median FVC after a six month follow up was 46.5%. Both drugs were well tolerated, but a dose reduction was needed in 2 patients due to rash and nausea. Three patients were intolerant to the treatment. Antifibrotic treatment may be a promising treatment in progressive non- IPF if no other options are available.
Galli et al. [23]	2017	Retrospective analysis	186	Nintedanib (57 patients) or pirfenidone (129 patients)	To examine the safety and tolerability Nintedanib or pirfenidone	Drug discontinuation occurred in 20.9% of patients on pirfenidone and 26.3% of patients on nintedanib due to adverse events. Adverse events that occurred most on pirfenidone were nausea (26.4%), rash and\or photosensitivity (14.7%), and dyspepsia/ GERD (12.4%). Diarrhea (52.6%) and nausea (29.8%) were reported most frequently with nintedanib therapy.
Oltmanns et al. [24]	2014	observational cohort	186	Nintedanib (57 patients) or pirfenidone (129 patients)	To examine the safety and tolerability Nintedanib or pirfenidone	Drug discontinuation occurred in 20.9% of patients on pirfenidone and 26.3% of patients on nintedanib due to adverse events. Adverse events that occurred most on pirfenidone were nausea (26.4%), rash and\or photosensitivity (14.7%), and dyspepsia/ GERD (12.4%). Diarrhea (52.6%) and nausea (29.8%) were reported most frequently with nintedanib therapy.

Table 1: Eligible studies

Discussion

Non-idiopathic pulmonary fibrosis is a severe type of pulmonary fibrosis [12]. The use of anti-fibrotic agents has been established in the treatment of idiopathic pulmonary fibrosis [17]. Because both idiopathic and non-idiopathic pulmonary fibrosis shares the same pathological manifestations, anti-fibrotic agents have been proposed to treat non-idiopathic pulmonary fibrosis [18]. However, their use for this indication still requires more evidence [21].

The aim of this systematic review is to examine the literature to identify the role of different anti-fibrotic agents in the management of non-idiopathic pulmonary fibrosis, in terms of their safety and efficacy for this indication. Eight studies [16-23] were eligible to be included in this review. Both nintedanib and pirfenidone were examined.

Six studies evaluated the safety and efficacy of pirfenidone for the management of non-idiopathic pulmonary fibrosis [16,18,20-23]. Lianos et al. [16] followed up patients on either pirfenidone or nintedanib for one year. Lianos et al. [16] revealed that about 8% of patients had a reduced FVC in spite of treatment, yet all other patients were improving or at least stable on treatment.

Torrisi et al. [18] also showed that the median FVC after six months of treatment with pirfenidone was 46%. Additionally, Matsumura et al. [20] showed that treatment of acute exacerbation using pirfenidone did not differ in survival after one month and three months. Yet, Matsumura et al. [20] concluded that pirfenidone might have a role in reducing inflammation in non-IPF [20].

Behr et al. [21] also revealed that pirfenidone could offer good control for FVC, though; this finding requires further confirmation [2]. Furthermore, Oltmanns et al. [23] showed that 66% of patients on pirfenidone were compliant with therapy. It is worth to mention that 62% of patients were stable, while the rest of the patients suffered from a decline in FVC [23].

As for safety and tolerability, Lianos et al. [16] showed that 14% of patients stopped the treatment due to intolerance, while gastrointestinal events (mainly diarrhea) were the most common side effects [16].

Torrisi et al. [18] also showed that the drug was well tolerated, with rash and nausea reported as the most common side effects. Behr et al. [21] also supported the findings of Torrisi et al. [18]. On the other hand, Galli et al. [22] showed that the discontinuation rate with pirfenidone was 20%, mainly due to nausea.

Turning to Nintedanib, Lianos et al. [16] demonstrated that the drug showed good control for FVC, with five patients stopped the medication due to intolerance. Also, Flaherty et al. [17] showed that nintedanib had an effective control for non-idiopathic pulmonary fibrosis.

Moreover, Flaherty et al. [17] found that nintedanib showed a significantly slower decline in FVC after one year follows up, compared to the placebo group. Torrisi et al. [18] also evaluated the efficacy of nintedanib. However, the findings are questionable because only one patient was recruited by Torrisi et al. [18] who used nintedanib.

Distler et al. [19] also evaluated the efficacy and safety of nintedanib through a randomized, double blind, placebo controlled study, and recruiting 576 patients on nintedanib. Distler et al. [19] showed that the decline in FVC in patients treated with nintedanib after one year was significantly lower than the placebo group [19].

Additionally, Galli et al. [22], through a retrospective study, revealed that the discontinuation rate of nintedanib was 26%.

As for the safety and tolerability of Nintedanib, Lianos et al. [16] showed that the most common side effect was an elevation in liver enzymes, followed by diarrhea and weight loss. However, Flaherty et al. [17] showed that the incidence of diarrhea was higher than the incidence of elevation of liver enzymes.

Distler et al. [19] also showed that diarrhea was the most common side effect reported in 75% of the patients. This was also supported by Galli et al. [22], were diarrhea and nausea were the most commonly reported side effect.

Additionally, the included trials had some limitations; some of the included studies were of retrospective nature, which could question the outcomes of their findings. Also, some studies included a small number of patients, which should be considered in any future studies [16,18,20,23].

Conclusion

From the present review, we can conclude that the use of pirfenidone and nintedanib in progressive non-idiopathic pulmonary fibrosis is promising and shows acceptable tolerability, yet, further studies are required to confirm these findings..

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