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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Is pirfenidone effective for idiopathic pulmonary fibrosis?

Authors: Alejandro Jeldres**[1,2]**, Gonzalo Labarca**[2,3,4,5]**

Affiliation:
[1] Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
[2] Proyecto Epistemonikos, Santiago, Chile
[3] Facultad de Medicina, Universidad San Sebastian, Concepción, Chile
[4] Departamento de Medicina Interna, Complejo Asistencial Dr. VÍctor RÍos Ruiz, Los Ángeles, Chile
[5] Programa de Salud Basada en Evidencia, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
E-mail: glabarcat@gmail.com

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Abstract

Idiopathic pulmonary fibrosis has an ominous prognosis and there are virtually no effective therapies. It has been suggested that pirfenidone, an antifibrotic agent, could change its course. Searching in Epistemonikos database, which is maintained by screening multiple databases, we identified 13 systematic reviews comprising nine trials addressing the question of this article, seven of which are randomized and whose results were analyzed in this summary. We combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. We concluded pirfenidone decreases disease progression and mortality in idiopathic pulmonary fibrosis. Although it is associated with frequent gastrointestinal and cutaneous adverse effects, these are generally not severe.

Problem

Idiopathic pulmonary fibrosis is a disease of low frequency and of uncertain etiology [1]. Its prognosis is similar to lung cancer and until the last decade no intervention had demonstrated survival benefits [2]. After diagnosis, survival decreases rapidly and several factors, including exacerbations, time to disease progression and deterioration in respiratory function are associated with poor prognosis [3],[4].

Pirfenidone [5-methyl-1-phenyl-2- [1H] -pyridone) is an oral antifibrotic, antioxidant and anti-inflammatory drug whose mechanism is based on acting as a scavenger of free hydroxyl radicals (OH-) and superoxide anions (O-), leading to decreased cytokine production (TNF-alpha, IFN-gamma, IL-1Beta, IL-6) and inhibiting fibroblast proliferation [5]. In 1999 the first published trial showed improvement in functional capacity, exacerbations and survival, after which other trials have been conducted [6],[7], which led to the FDA's approval in 2014 for its use in the treatment of idiopathic pulmonary fibrosis [8].

Methods

We used Epistemonikos database, which is maintained by screening multiple databases, to identify systematic reviews and their included primary studies. With this information we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages
- Pirfenidone decreases disease progression and mortality in idiopathic pulmonary fibrosis.
- Pirfenidone has frequent, but not severe, gastrointestinal and cutaneous adverse effects.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found 13 systematic reviews reported in 14 references [2],[9],[10], [11],[12],[13],[14],[15],[16],[17],[18],[19],[20],[21] comprising nine primary studies, reported in 10 references [6],[22],[23],[24],[25],[26], [27],[28],[29],[30], including seven randomized controlled trials published in eight references [22],[23],[24],[25],[26],[27],[29],[30]. Two randomized trials [30],[31] were not considered in this summary because the study population did not correspond to that of the question under investigation. This table and the overall summary are based on the five randomized trials relevant to the question.
What types of patients were included	All trials included patients diagnosed with idiopathic pulmonary fibrosis according to the standards of the American Thoracic Society of 2011. Patients ranged from 20 to 80 years of age. One trial included patients with PaO2 ≥ 70 mmHg at rest and SpO2 ≤ 90% on exercise [25], two trials included patients diagnosed with pulmonary fibrosis in the past year [24],[25], while three others included them if the diagnosis had been made in the past four years [22],[23],[26],[27]. Three trials included patients with functional capacity between 50 and 90% [22],[23],[26],[27], three trials included patients with DLCO> 30% [22],[23],[26],[27], two trials included patients with walk test in six minutes higher or equal to 150 m [23],[26],[27] and one trial included patients with FEV1 / FVC> 70%. [22].
What types of interventions were included	All trials used pirfenidone as monotherapy. Three trials used pirfenidone at doses of 2,400 mg daily [22],[23],[26],[27] and two trials used pirfenidone at doses of 1,800 mg daily [24],[25].Two trials administered concomitant treatment with prednisolone at doses of less than 10 mg daily [24],[25]. All trials compared against placebo.
What types of outcomes were measured	The different systematic reviews identified grouped the outcomes as follows: • Mortality from any cause and related to idiopathic pulmonary fibrosis • Acute exacerbations • Disease progression at 52 weeks ((Drop in FVC> o = 10%, drop in DLCO > o = 15%, death) • Change in walk test in six minutes • Change in predicted functional vital capacity • Non-serious adverse events (change in aminotransferases and related to the skin) and severe • Quality of life • Scale of dyspnea

Summary of findings

The information on the effects of pirfenidone is based on five randomized trials [22],[23],[24], [25],[26],[27] involving 1,567 patients. All trials reported mortality, two trials [24],[25] reported acute exacerbations and four trials [22],[23],[24],[26],[27] reported progression-free survival. The summary of findings is as follows:

- Pirfenidone decreases mortality in idiopathic pulmonary fibrosis. The certainty of the evidence is high.
- Pirfenidone decreases disease progression in idiopathic pulmonary fibrosis. The certainty of the evidence is high.
- Pirfenidone might reduce the risk of acute exacerbations, but the certainty of the evidence is low.
- Pirfenidone has frequent, but not severe, gastrointestinal side effects. The certainty of the evidence is high.
- Pirfenidone has frequent, but not severe, cutaneous adverse effects. The certainty of the evidence is high.

Pirfenidone for idiopathic pulmonary fibrosis				
Patients	Adults with idiopathic pulmonary fibrosis			
Intervention	Pirfenidone			
Comparison	Placebo			
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT pirfenidone	**WITH pirfenidone**		
	Difference: patients per 1000			
Mortality	62 per 1000	33 per 1000	RR 0.53 (0.33 a 0.84)	⊕⊕⊕⊕ High
	Difference: 29 patients less per 1000 (Margin of error: 10 a 41 less)			
Disease progression At 52 weeks	384 per 1000	323 per 1000	RR 0.84 (0.75 a 0.94)	⊕⊕⊕⊕ High
	Difference: 61 patients less per 1000 (Margin of error: 23 to 96 less)			
Acute exacerbations	65 per 1000	35 per 1000	RR 0.54 (0.22 a 1.33)	⊕⊕◯◯[1,2] Low
	Difference: 30 patients less per 1000 (Margin of error: 51 less to 21 more)			
Gastrointestinal adverse events	30 per 1000	70 per 1000	RR 2.33 (1.54 a 3.52)	⊕⊕⊕⊕ High
	Difference: 40 patients more per 1000 (Margin of error: 16 a 76 more)			
Non-serious cutaneous adverse events	41 per 1000	148 per 1000	RR 3.65 (2.58 a 5.15)	⊕⊕⊕⊕ High
	Difference: 107 patients more per 1000 (Margin of error: 64 a 168 more)			

RR= Risk ratio.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article).

* The risk **WITHOUT pirfenidone** is based on the risk in the control group of the trials. The risk **WITH pirfenidone** (and its margin of error) is calculated from relative effect (and its margin of error)

[1] The certainty of the evidence was downgraded because of inconsistency (I^2 = 81%).
[2] The certainty of the evidence was downgraded because of imprecision, since the confidence interval includes no effect. Considering the effect on the other outcomes, the most likely hypothesis is there is an effect on this outcome, but the studies are not able to prove this statistically because they have a low number of events.

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

- This evidence applies to adult patients diagnosed with idiopathic pulmonary fibrosis.
- Although the trials evaluated patients with mild to moderate disease, we believe that it is not reasonable to extrapolate their results to those with more advanced forms of disease or those with diffuse pulmonary disease of different type from idiopathic pulmonary fibrosis (condisering the high cost of this therapy, it is recommended to evaluate lung transplantation as the alternative).

About the outcomes included in this summary

- The outcomes selected for the summary of findings are those considered critical in the decision making by the authors of this article.
- While some reviews put an important emphasis in functional outcomes, the inclusion of these would not change decision-making, since they only reinforce there is a clear benefit. For example, 108 fewer patients experienced deterioration in the 6-minute walking test with pirfenidone (95% CI 63 to 150 less, RR 0.74 [95% CI 0.64 to 0.85]; high certainty).

Balance between benefits and risks, and certainty of the evidence

- Pirfenidone shows clear benefit on the most important outcomes, and adverse effects, although frequent, are not severe.
- The balance between benefits and risks is clearly favorable to the use of this intervention.

What would patients and their doctors think about this intervention

- The evidence presented in this summary should lead most patients and clinicians to consider its use.
- It is important to discuss the adverse effects in advance, and if they appear, to address them early, in order to reinforce adherence to treatment.

Resource considerations

- Cost is probably one of the major limitations in the use of this drug. It is a high cost intervention, which is not yet available in many countries.
- The cost/effectiveness in the settings where it has been assessed appears favorable [12]. However, in places where the cost of the drug is high, a formal evaluation of this factor is desirable, especially if there are limited resources.

Differences between this summary and other sources

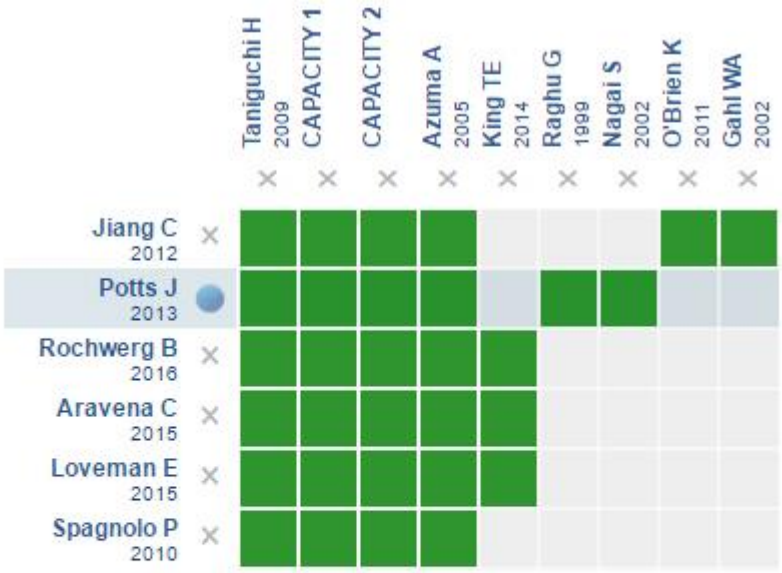
- The conclusions of our summary are consistent with those of the systematic reviews identified.
- Our summary is consistent with the main clinical guideline in this area, which suggests the use of pirfenidone, although the recommendation is weak [31]. This is likely to be because it does not incorporate a significant proportion of the evidence synthesized in this article.

Could this evidence change in the future?

- The probability that future evidence changes the conclusions presented in this summary is very low, due to the certainty of the existing evidence.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version:** Pirfenidone for idiopathic pulmonary fibrosis

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here http://dx.doi.org/10.5867/medwave.2014.06.5997.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

References

1. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011 Mar 15;183(6):788-824 | CrossRef | PubMed |
2. Spagnolo P, Del Giovane C, Luppi F, Cerri S, Balduzzi S, Walters EH, et al. Non-steroid agents for idiopathic

pulmonary fibrosis. Cochrane Database Syst Rev. 2010 Sep 8;(9):CD003134 | CrossRef | PubMed |
3. Vancheri C, Failla M, Crimi N, Raghu G. Idiopathic pulmonary fibrosis: a disease with similarities and links to cancer biology. Eur Respir J. 2010 Mar;35(3):496-504 | CrossRef | PubMed |
4. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2006 Oct 1;174(7):810-6 | PubMed |
5. Margaritopoulos GA, Vasarmidi E, Antoniou KM. Pirfenidone in the treatment of idiopathic pulmonary fibrosis: an evidence-based review of its place in therapy. Core Evid. 2016 Jul 1;11:11-22 | CrossRef | PubMed |
6. Raghu G, Johnson WC, Lockhart D, Mageto Y. Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: results of a prospective, open-label Phase II study. Am J Respir Crit Care Med. 1999 Apr;159(4 Pt 1):1061-9 | PubMed |
7. Nice.org.uk. [Online]. Available from: https://www.nice.org.uk/guidance/ta282/documents/idiopathic-pulmonary-fibrosis-pirfenidone-pre-meeting-briefing2 [Accessed 28 November 2016]. | Link |
8. Fda.gov. [Online]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022535s000lbl.pdf. [Accessed 28 November 2016]. | Link |
9. Loveman E, Copley VR, Scott DA, Colquitt JL, Clegg AJ, O'Reilly KM. Comparing new treatments for idiopathic pulmonary fibrosis--a network meta-analysis. BMC Pulm Med. 2015 Apr 18;15:37 | CrossRef | PubMed |
10. Loveman E, Copley VR, Colquitt JL, Scott DA, Clegg AJ, Jones J, et al. The effectiveness and cost-effectiveness of treatments for idiopathic pulmonary fibrosis: systematic review, network meta-analysis and health economic evaluation. BMC Pharmacol Toxicol. 2014 Nov 19;15:63 | CrossRef | PubMed |
11. Atkins CP, Loke YK, Wilson AM. Outcomes in idiopathic pulmonary fibrosis: a meta-analysis from placebo controlled trials. Respir Med. 2014 Feb;108(2):376-87 | CrossRef | PubMed |
12. Loveman E, Copley VR, Colquitt J, Scott DA, Clegg A, Jones J, et al. The clinical effectiveness and cost-effectiveness of treatments for idiopathic pulmonary fibrosis: a systematic review and economic evaluation. Health Technol Assess. 2015 Mar;19(20):i-xxiv, 1-336 | CrossRef | PubMed |
13. Aravena C, Labarca G, Venegas C, Arenas A, Rada G. Pirfenidone for Idiopathic Pulmonary Fibrosis: A Systematic Review and Meta-Analysis. PLoS One. 2015 Aug 26;10(8):e0136160 | CrossRef | PubMed |
14. Canestaro WJ, Forrester SH, Raghu G, Ho L, Devine BE. Drug Treatment of Idiopathic Pulmonary Fibrosis: Systematic Review and Network Meta-Analysis. Chest. 2016 Mar;149(3):756-66 | CrossRef | PubMed |
15. Bajwah S, Ross JR, Peacock JL, Higginson IJ, Wells AU, Patel AS, et al. Interventions to improve symptoms and quality of life of patients with fibrotic interstitial lung disease: a systematic review of the literature. Thorax. 2013 Sep;68(9):867-79 | CrossRef | PubMed |
16. Rochwerg B, Neupane B, Zhang Y, Garcia CC, Raghu G, Richeldi L, et al. Treatment of idiopathic pulmonary fibrosis: a network meta-analysis. BMC Med. 2016 Feb 3;14:18 | CrossRef | PubMed |
17. Rogliani P, Calzetta L, Cavalli F, Matera MG, Cazzola M. Pirfenidone, nintedanib and N-acetylcysteine for the treatment of idiopathic pulmonary fibrosis: A systematic review and meta-analysis. Pulm Pharmacol Ther. 2016 Oct;40:95-103 | CrossRef | PubMed |
18. Cooper K, Mendes D, Picot, J, Loveman E. Pirfenidone for the treatment of idiopathic pulmonary fibrosis: A Single Technology Appraisal. SHTAC, 2012. Available in http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0007/82591/ERGReport-09-135-01.pdf | Link |
19. Potts J, Yogaratnam D. Pirfenidone: a novel agent for the treatment of idiopathic pulmonary fibrosis. Ann Pharmacother. 2013 Mar;47(3):361-7 | CrossRef | PubMed |
20. Institute for Quality and Efficiency in Health Care. Pirfenidone: Benefit assessment according to § 35a Social Code Book V; extract of dossier assessment; Commission No. A11-18 [online]. 12.1.2011 | Link |
21. Jiang C, Huang H, Liu J, Wang Y, Lu Z, Xu Z. Adverse events of pirfenidone for the treatment of pulmonary fibrosis: a meta-analysis of randomized controlled trials. PLoS One. 2012;7(10):e47024 | CrossRef | PubMed |
22. King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014 May 29;370(22):2083-92 | CrossRef | PubMed |
23. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet. 2011 May 21;377(9779):1760-9 | CrossRef | PubMed |
24. Taniguchi H, Ebina M, Kondoh Y, Ogura T, Azuma A, Suga M, et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J. 2010 Apr;35(4):821-9 | CrossRef | PubMed |
25. Azuma A, Nukiwa T, Tsuboi E, Suga M, Abe S, Nakata K, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2005 May 1;171(9):1040-7 | PubMed |
26. CAPACITY 1. Intermune. A randomized, double-blind, placebo-controlled, phase 3 study of the safety and efficacy of pirfenidone in patients with idiopathic pulmonary fibrosis; study PIPF-006; clinical study report [unpublished]. 2009
27. CAPACITY 2. Intermune. A randomized, double-blind, placebo-controlled, phase 3, three-arm study of the safety and efficacy of pirfenidone in patients with idiopathic pulmonary fibrosis: study PIPF-004; clinical study report [unpublished]. 2009.
28. Nagai S, Hamada K, Shigematsu M, Taniyama M, Yamauchi S, Izumi T. Open- label compassionate use one year-treatment with pirfenidone to patients with chronic pulmonary fibrosis. Intern Med. 2002 Dec;41(12):1118-23 | PubMed |
29. O'Brien K, Troendle J, Gochuico BR, Markello TC, Salas J, Cardona H, et al. Pirfenidone for the treatment of

Hermansky-Pudlak syndrome pulmonary fibrosis. Mol Genet Metab. 2011 Jun;103(2):128-34 | CrossRef | PubMed |
30. Gahl WA, Brantly M, Troendle J, Avila NA, Padua A, Montalvo C, et al. Effect of pirfenidone on the pulmonary fibrosis of Hermansky-Pudlak syndrome. Mol Genet Metab. 2002 Jul;76(3):234-42 | PubMed |
31. Raghu G, Rochwerg B, Zhang Y, Garcia CA, Azuma A, Behr J, et al; American Thoracic Society.; European Respiratory society.; Japanese Respiratory Society.; Latin American Thoracic Association.. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. Am J Respir Crit Care Med. 2015 Jul 15;192(2):e3-19 | CrossRef | PubMed |

Author address:
[1] Facultad de Medicina
Pontificia Universidad Católica de Chile
Diagonal Paraguay 476
Santiago Centro
Chile