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Prognosis of adults with idiopathic pulmonary fibrosis without treatment or without effective therapies (Protocol)

Khor YH, Ng Y, Goh NSL, McDonald CF, Holland AE

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[Prognosis Protocol]

Prognosis of adults with idiopathic pulmonary fibrosis without treatment or without effective therapies

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ABSTRACT

This is a protocol for a Cochrane Review (Prognosis). The objectives are as follows:

Primary objective

To assess overall prognosis for people with idiopathic pulmonary fibrosis (IPF) in terms of mortality and survival outcomes without therapy or without effective therapies

Secondary objectives

- To assess the overall prognosis for people with IPF for respiratory-related outcomes without therapy or without effective therapies

- To assess the change in overall prognosis of people with IPF in terms of mortality and survival outcomes without therapy or without effective therapies based on different diagnostic criteria according to the consensus guidelines

BACKGROUND

Description of the condition

Idiopathic pulmonary fibrosis (IPF), the most common of the idiopathic interstitial pneumonias, is a devastatingly progressive pulmonary parenchymal disease. It is characterised histopathologically by a heterogenous appearance with areas of marked fibrosis and honeycombing alternating with areas of relatively normal

parenchyma (ATS 2000; ATS 2002; Raghu 2011). Radiologically, it typically manifests as a usual interstitial pneumonia pattern with reticular abnormality and honeycombing with possible traction bronchiectasis in a predominant subpleural and basal distribution (Raghu 2011). People with IPF commonly experience disabling symptoms, including dyspnoea, cough and fatigue, causing exercise limitation and impaired quality of life.

Idiopathic pulmonary fibrosis is the first or second most common interstitial lung disease encountered in medical practice (Coultas 1996; Thomeer 2001; Ohno 2008; Karakatsani 2009; Musellim 2014; Bando 2015). A population-based study of IPF in the United States, based on diagnostic criteria of the consensus statement by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) in 2000 (ATS 2000), reported a prevalence of 27.9 to 63.0 per 100,000 people (Fernández 2010). According to a recent report from the British Lung Foundation, the prevalence of IPF in the United Kingdom was 50 per 100,000 people in 2012 (British Lung Foundation 2016), which was higher than the estimated prevalence of 15 to 25 cases per 100,000 people suggested by the National Institute for Health and Care Excellence (NICE 2015). Both the incidence and prevalence rates of IPF increase with age across different study populations, even in countries with low disease prevalence (Raghu 2006; Lai 2012; Annesi-Maesano 2013; Musellim 2014; Natsuizaka 2014; Esposito 2015; Hopkins 2016). More importantly, the incidence of IPF appears to be rising over time (Raghu 2006; Navaratnam 2013). However, there are significant ethnic and geographic variations in its incidence. A recent systematic review of population-based studies in IPF estimated a conservative incidence range of 3 to 9 cases per 100,000 population per year for Europe and North America, in comparison to 0.4 to 3.8 cases per 100,000 population per year for Asia and South America (Hutchinson 2015).

The health and economic impacts of IPF are substantial. In the United States, healthcare utilisation by people with IPF was approximately twice as high as that by matched controls (Collard 2012; Wu 2015), with an estimated all-cause healthcare cost of $59,379 per person in 2011 (Raimundo 2016). The average number of annual outpatient visits per person with IPF was 18.5, with 5.7 being respiratory-related (Raimundo 2016). Approximately 38% of patients had at least one hospitalisation each year (Raimundo 2016; Yu 2016). Thus, hospitalisation expenditure for people with IPF is high with an estimated financial burden of £16.2 million in 2010 in the United Kingdom (Navaratnam 2013). More recent studies reported comparable significant hospitalisation costs of $16,042 per admission between 2009 and 2011 in the United States (Mooney 2017) and EURO3224 to EURO6513 per admission between 2008 and 2013 in France (Cottin 2017). Given the significant global burden of IPF in both disease and economic terms, understanding its prognosis is important for healthcare planning and allocation of resources.

During the last decade, major respiratory societies, including the ATS and the ERS, published a consensus statement for the diagnosis and treatment of IPF (ATS 2000; ATS 2002). This consensus statement has been updated more recently (Raghu 2011; Travis 2013; Raghu 2015). With increasing understanding and knowledge of IPF, diagnostic criteria and methods for IPF have changed considerably over time, from a predominantly histopathological assessment to a multidisciplinary team approach based on clinical, radiologic and histopathologic correlation. Idiopathic pulmonary fibrosis has previously been reported to have a median survival of 2 to 3 years from time of diagnosis (Bjoraker 1998; Nicholson 2000; King 2001; Flaherty 2002; Nathan 2011). However, information about the long-term prognosis of patients with IPF has been derived mostly from studies performed prior to the publication of the recent consensus statements (Raghu 2011; Travis 2013; Raghu 2015). It is possible that the prognosis for IPF may have changed over time due to changes in diagnostic criteria, rather than necessarily because of any change in the nature of the disease process itself, however this hypothesis has not been examined.

Why it is important to do this review

A recent study in patients with interstitial lung disease attending pulmonary rehabilitation, including those with IPF, found that patients wish to have more information about their prognosis (Holland 2015). Accurate prognostic information is essential in order to assist patients and their families in planning for the future. Treatment options for IPF are generally limited. Nevertheless, with recent improved understanding of its disease mechanisms, new therapies targeting different cellular molecules have been designed and trialled. Among those, pirfenidone and nintedanib have been shown to significantly slow disease progression and potentially improve survival in IPF (King 2014; Richeldi 2014). A clearer understanding of the prognosis of IPF is crucial in order for clinicians to be able to properly evaluate the potential impacts of these and other new approaches in the management paradigm of IPF. Knowledge of prognosis is also of vital importance for thoughtful discussion with patients regarding expectations, in order to ensure the timely offer of supportive care and avoidance of costly, unnecessary therapies with potentially significant adverse effects.

OBJECTIVES

Primary objective

To assess overall prognosis for people with idiopathic pulmonary fibrosis (IPF) in terms of mortality and survival outcomes without therapy or without effective therapies

Secondary objectives

- To assess the overall prognosis for people with IPF for respiratory-related outcomes without therapy or without effective therapies

- To assess the change in overall prognosis of people with IPF in terms of mortality and survival outcomes without therapy or without effective therapies based on different diagnostic criteria according to the consensus guidelines

METHODS

Criteria for considering studies for this review

Types of studies

- Any retrospective or prospective cohort study assessing overall survival or mortality as an outcome in patients with IPF without therapy or without effective therapies
- Any randomised controlled trial (RCT) assessing the role of investigational treatment versus no treatment or placebo or best supportive therapy in patients with IPF - only the no treatment or placebo or best supportive therapy arm will be included
- Definition of effective therapies: nintedanib, pirfenidone
- Follow-up period of at least 12 months
- Exclusion criteria:
    - For RCT: active therapy arms

Types of participants

Participants aged ≥ 18 years with a diagnosis of IPF, diagnosed according to investigator definitions, will be included. No exclusions will be based on gender, presence or absence of histological diagnosis, or physiological status.

Types of outcome measures

Primary outcomes

- Overall mortality: proportion of mortality (percentage) (at 1 year to < 2 years, 2 years to < 5 years, 5 years or greater)
- Overall survival: mean survival (months)

Secondary outcomes

- Progression-free survival (months)
- Respiratory-specific mortality (percentage) (at 1 year to < 2 years, 2 years to < 5 years, 5 years or greater)
- Change in forced vital capacity (FVC) (percentage predicted or litres) (at 1 year to < 2 years, 2 years to < 5 years, 5 years or greater)
- Change in diffusion capacity for carbon monoxide (DLCO) (percentage predicted or mmol/min/kPa) (at 1 year to < 2 years, 2 years to < 5 years, 5 years or greater)
- Proportions of patients with an absolute decline in FVC of 10% or more (percentage) (at 1 year to < 2 years, 2 years to < 5 years, 5 years or greater)
- Proportions of patients with an absolute decline in DLCO of 15% or more (percentage) (at 1 year to < 2 years, 2 years to < 5 years, 5 years or greater)
- Dyspnoea: all measures of dyspnoea used will be considered (at 1 year to < 2 years, 2 years to < 5 years, 5 years or greater)
- Health-related quality of life (at 1 year to < 2 years, 2 years to < 5 years, 5 years or greater): either generic or disease-specific quality of life instruments. All instruments used will be considered.
- Six-minute walk distance (m) (at 1 year to < 2 years, 2 years to < 5 years, 5 years or greater)

A decline in FVC of 10% or more and a decline in DLCO of 15% or more are selected because these features are accepted as significant physiologic declines associated with increased risk of mortality in IPF (Raghu 2011).

Search methods for identification of studies

Electronic searches

We will search for relevant studies in the following databases.

- MEDLINE (Ovid)
- Embase (Ovid)
- CINAHL (EBSCO)
- PubMed
- CENTRAL (part of the Cochrane Library)

To identify RCTs, we will use the Cochrane Highly Sensitive Search strategy (Lefebvre 2011). To identify retrospective and cohort studies assessing survival or mortality we will use a prognostic search filter based on work by Wilczynski 2004. These sets of search terms will be combined with a set of disease-specific terms. For the full MEDLINE strategy see Appendix 1. This strategy will be adapted for use in the other databases. All databases will be searched from their inception to the present, and there will be no restriction on language of publication.

Searching other resources

- Reference lists of included studies and related review papers will be handsearched for qualifying studies.
- Clinical trial registries will be reviewed to search for relevant planned, ongoing and unpublished trials.
- Annual conference abstracts from the ATS, the ERS, the Asian Pacific Society of Respirology, and the Thoracic Society of Australia and New Zealand will be reviewed for relevant studies.
- Authors of the consensus statements on IPF (ATS 2000; ATS 2002; Raghu 2011; Travis 2013; Raghu 2015) will be contacted for unpublished studies.

Data collection

Selection of studies

Data management and analysis will be conducted in RevMan according to the methodology described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).
Two review authors (YHK and YN) will independently review and code the literature searches to identify potentially relevant trials for full review by examining titles, abstracts and keyword fields as follows.

1. Include: a study that meets all review criteria
2. Unclear: a study that appears to meet some review criteria, but available information is insufficient to determine relevance
3. Exclude: a study that does not meet all review criteria

A full-text copy of all studies in categories 1 and 2 will be retrieved and reassessed independently by two review authors (YHK and YN) to decide on study inclusion. Any disagreement as to which papers to include will be resolved by consensus. The agreement of the decisions between the two review authors will be calculated using simple kappa statistics.

Data extraction and data management

Data extraction will be performed independently by two review authors (YHK and YN) using standardised study assessment and data extraction forms. Data extracted will include study characteristics (inclusion and exclusion criteria; study setting; year of study; funding source; duration of study; number of participants; baseline participant characteristics) and outcome data from all follow-up time points (measures of central tendency and dispersion for continuous variables, number of participants in each outcome category for dichotomous or categorical variables). For RCT, only data from the no treatment or placebo or best supportive therapy arm will be extracted and included. For each study, the two sets of data extracted by two review authors will be cross-checked. Disagreement will be resolved by consensus or a third review author if required. If necessary, study authors will be contacted for clarification or to provide details of missing data where possible.
Median for outcomes reported in Kaplan-Meier curve will be extracted using the published methods (Guyot 2012). For continuous data, measures of central tendency will be converted to means and measures of dispersion will be converted to standard errors using the published methods (Hozo 2005; Higgins 2011).

Assessment of methodological quality

To evaluate methodological quality, two review authors (YHK and YN) will independently perform a 'Risk of bias' assessment for included studies using a table with predefined criteria from existing tools and other published studies (see Table 1) (Laupacis 1994; Hayden 2006; Stang 2010; Higgins 2011; Wao 2013). Disagreement will be resolved by consensus. Authors of included studies will be contacted for clarification if inadequate information is available for review authors to judge the risk of bias. If the study authors are unable to be contacted for clarification, the criteria will be listed as 'unclear'.

Investigation/description of heterogeneity

The magnitude of heterogeneity will be measured through the I^2 statistic, as described in the *Cochrane Handbook* (Higgins 2011). The thresholds for I^2 values will be as follows: low (25% to 49%), moderate (50% to 74%), and high ($\geq$ 75%)

Data synthesis

For the purpose of meta-analysis, logistic meta-analysis will be used for dichotomous outcomes and linear meta-analysis will be used for continuous outcomes. The analyses will be performed using a random-effects generic inverse variance model.
If meta-analysis is not appropriate (for example there is significant heterogeneity in reported outcome measures or follow-up periods, or a small number of included studies with available data), the results will be presented qualitatively.

Sensitivity analysis

Sensitivity analysis will be performed based on the types of study design (cohort studies versus RCT, retrospective cohort studies versus prospective cohort studies).
Subgroup analyses will be performed to explore possible sources of heterogeneity. A priori subgroup analyses will consist of the following.

- Diagnostic criteria for IPF
  - Group 1 - ATS/ERS Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment. International Consensus Statement 2000 (ATS 2000)
  - Group 2 - An official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management 2011 (Raghu 2011)

○ Group 3 - Other definitions (Including physicians' diagnosis)

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Assessing the risk of bias

Criteria	High risk of bias	Low risk of bias	Unclear/other
Sample	Clinical	Population	Unclear
Recruitment	Retrospective	Prospective	Unclear
Selection criteria for participants	No	Yes	Unclear
Baseline characteristics of participants	No	Yes	Unclear
Follow-up percentage (if RCT)	< 80%	≥ 80%	Unclear
			Not applicable
Follow-up duration	< 1 year	≥ 1 year	Unclear
Reason lost to follow-up	No	Yes	Unclear

Table 1. Assessing the risk of bias (*Continued*)

Timing of diagnosis	At the conclusion of the study	At baseline or before recruitment to study	Unclear
Blinding	Not blinded	Blinding adequate	Unclear
Outcome described a priori	No	Yes	Unclear
Intention-to-treat analysis (if RCT)	No	Yes	Unclear
			Not applicable
Adequate description of statistical analysis	No	Yes	Unclear

APPENDICES

Appendix 1. MEDLINE (Ovid) search strategy

1. Idiopathic Pulmonary Fibrosis/
2. ((pulmonary$ or lung$ or alveoli$) adj2 (fibros$ or fibrot$)).tw.
3. 1 or 2
4. Randomized Controlled Trial.pt.
5. (randomized or randomised).ab,ti.
6. placebo.ab,ti.
7. dt.fs.
8. randomly.ab,ti.
9. trial.ab,ti.
10. groups.ab,ti.
11. or/4-10
12. follow-up studies.sh.
13. cohort.tw.
14. exp mortality/
15. course$.tw.
16. prognos$.tw.
17. predict$.tw.
18. incidence.sh.
19. survival analysis/
20. or/12-19
21. 3 and (11 or 20)
22. Animals/
23. Humans/
24. 22 not (22 and 23)
25. 21 not 24

CONTRIBUTIONS OF AUTHORS

Coordinating the review: YHK

Drafting protocol and review: YHK, NG, CM, AH

Designing search strategies: YHK, Cochrane Airways Group Information Specialist (Elizabeth Stovold)

Data collection for the review: YHK, YN

Data analysis: YHK, AH

Data interpretation: YHK, NG, CM, AH

DECLARATIONS OF INTEREST

YHK: None known

YN: None known

NG: None known

AH: None known

CM has received personal fees for participation in advisory boards for Pfizer and Novartis; has participated in advisory board for Astra Zeneca (no fee); has received speakers fees from GSK and Novartis; and has received in-kind support for a research project from Air Liquide.

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