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The effect of statin therapy on disease-related outcomes in idiopathic pulmonary fibrosis: a systematic review and meta-analysis

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Abstract

Background

Idiopathic pulmonary fibrosis is a progressive disease and antifibrotic therapies do not reverse existing fibrosis. There has been emerging evidence of potential role for statins in idiopathic pulmonary fibrosis. The aim of this review is to synthesise the evidence on the efficacy of statins in idiopathic pulmonary fibrosis, focusing on associations with all-cause mortality, disease specific mortality and change in pulmonary function.

Methods

Medline and Embase were reviewed to identify relevant publications. Studies were selected if they examined disease related outcomes including mortality, pulmonary function and adverse events in people with idiopathic pulmonary fibrosis receiving statin therapy.

Results

Five studies with a total of 3407 people with IPF were selected and analysed. The overall risk of bias of five included studies was moderate to serious. In the fixed effect meta-analysis, statin use was associated with a reduction in mortality (RR 0.8; 95% CI 0.72-0.99). However, in the random effects model, there was no longer any significant association between statin use and all-cause mortality (RR 0.87; 95% CI 0.68-1.12). There was no statistically significant association between statin use and decline in FVC % predicted.

Conclusion:

There is currently insufficient evidence to conclude the effect of statin therapy on disease-related outcomes in idiopathic pulmonary fibrosis. Considering the limitations of available literature, we would recommend a prospective cohort study with capture of dosage and preparation of statin, statin adherence and use of concurrent antifibrotic treatment.

PROSPERO registration number: CRD42019122745

Keywords: idiopathic pulmonary fibrosis, statin, mortality

Introduction

Idiopathic pulmonary fibrosis (IPF), the most common form of interstitial lung diseases (ILD), is a life-limiting condition that causes 5000 deaths each year in the UK, and the incidence is increasing in the UK[1]. The pathogenesis of IPF is poorly understood. It is hypothesised that alveolar epithelial cell injury triggers release of cytokines such as transforming growth factor beta 1 (TGFß1), platelet-derived growth factor (PDGF), and tumour necrosis factor (TNF) α [2,3]. Release of these cytokines result in proliferation of fibroblast and fibroblast differentiation into the myofibroblast [4], which in turn result in extensive extracellular matrix formation and contraction of scar tissue [5,6]. Antifibrotic agents, pirfenidone and nintedanib, slow decline in pulmonary function, however they do not reverse existing fibrosis.

Statins are well known for its lipid-lowering properties through inhibition of HMG-CoA reductase. Statins also exert immunomodulatory and anti-inflammatory effects via poorly understood mechanisms [7]. In vitro studies have shown that simvastatin overrides the effect of TGFß1 and inhibits connective tissue growth factor (CTGF) gene and protein expressions in IPF-derived fibroblasts [4]. Simvastatin also decreases alpha smooth muscle actin (α-SMA), a marker of myofibroblast formation, expression via inhibition of Rho pathway [4].

Existing studies have reported divergent findings on the link between statin use and fibrotic disease processes. Previously, statin use was considered to be a potential cause of interstitial lung diseases [8,9] and data from COPDGene study showed association between statin use and interstitial lung abnormalities and exacerbated bleomycin induced fibrosis in mice pre-treated with pravastatin [8]. However, another study showed that pravastatin reduced bleomycin-induced pulmonary fibrosis [10] and a similar effect was observed with atorvastatin in mouse model [11]. Furthermore, a large cohort study conducted in Canada did not show any association between statin use and the incidence of ILD [12]. However, post hoc analysis of data from the CAPACITY [13] and ASCEND [14] trials indicated that statin use was potentially associated with favourable disease-related outcomes in patient with IPF [15].

Additionally, there has been emerging evidence that statin use may be associated with a favourable outcome in terms of fibrosis progression in other conditions. In chronic hepatitis patients, statin therapy showed a dose-dependent decreased risk of cirrhosis development [16,17] and lower the risk of decompensated liver disease [18,19]. However, a recent randomised controlled trial in hypertrophic cardiomyopathy did not reveal an association between atorvastatin therapy and left ventricular (LV)

mass regression or improvement in LV diastolic function [20].

The potential effect of statin in interstitial fibrosis remains unclear, and to date a systematic review has not been conducted. IPF remains a progressive disease and new antifibrotic therapies do not reverse existing fibrosis. Therefore, evaluating the effect of the potential adjuvant therapy may offer new approaches in the management of IPF. Hence, we aimed to synthesise the evidence on the efficacy of statins in IPF, focusing on association between statin use and all-cause mortality, disease-specific mortality and decline in pulmonary function test.

Methods

Study design

This systematic review is registered with PROSPERO, registration number: CRD42019122745

We followed PRISMA reporting standards [21]. The initial search was conducted independently by two reviewers (JK and KB) between January 2019 and February 2019 and an update search was conducted in March 2020.

Eligibility criteria

Studies were considered for inclusion if (1) they involved adult participants with diagnosis of IPF (2) intervention involving any form of statins irrespective of duration (3) controls including placebo, no statin therapy or other IPF therapy (4) reporting disease related outcomes including mortality, pulmonary function and adverse events. Eligible study design included observational studies and randomised controlled studies. We excluded review papers, comments editorials and non-English language articles. We also chose not to consider conference abstracts and grey literature because their data may not have undergone full peer review and there would not be sufficient detail for us to conduct our own rigorous quality assessment.

Search strategy

Medline and Embase were reviewed to identify relevant publications [22]. The initial search strategy was developed in consideration of previously published systematic reviews [23-25]. (Appendix 1) The reference

lists and citations of relevant studies were screened, and we searched for studies referencing the included studies to capture any additional studies.

Data collection

The studies were screened by title and abstract by two reviewers (JK and KB) independently using the Rayyan online platform (rayyan.qcri.org). Data was extracted by two reviewers (JK and KB) onto data collection form using the customised Cochrane data collection form for intervention review for RCTs and non-RCTs [26]. Any disagreement between reviewers were discussed until resolved.

Risk of bias

Risk of bias assessment was independently performed by two reviewers (JK and KB). For non-randomized studies, Risk Of Bias In Non-randomized Studies – of Intervention (ROBINS-1) [27] was used. ROBINS-1 tool assesses risk of bias due to 1) confounding 2) selection of participants into the study 3) classification of interventions 4) intended intervention 5) missing data 6) measurement of outcomes 7) selection of the reported results. It classifies risk of bias 'low', 'moderate', 'serious', 'critical' and 'no information'. Overall risk of bias is judged to be at low risk of bias if low risk of bias for all domains, at moderate risk of bias if low or moderate risk of bias in all domains, at serious risk of bias if at serious risk of bias in at least one domain, and at critical risk of bias if at critical risk of bias in at least one domain. A third reviewer was not required as there was no disagreement between reviewers.

Summary measures

Primary outcome measurements was all-cause mortality, whilst secondary outcomes included disease-specific mortality and change in pulmonary function in people with IPF. We also explored adverse events, change in patient reported outcome measurements and hospital admissions.

Synthesis of results

Where more than one study reported the same outcome measured in similar way, a meta-analysis was undertaken. Alternatively, a narrative synthesis of the findings was conducted. RevMan software [28] were used for statistical analysis. For meta-analysis, we calculated a risk ratio and 95% confidence intervals using both fixed effect model and random effect model. Heterogeneity of included studies were quantified using the chi-squared test (Q test) and I-squared statistic. I^2 was considered might not

important if 0% to 40%, may represent moderate heterogeneity if 30% to 60%, may represent substantial heterogeneity if 50% to 90%, considerable heterogeneity if 75% to 100% [29].

Results

Study selection and characteristics of the include studies

The search identified 782 publications with 48 full text articles reviewed. Five studies were selected for inclusion. (figure1) Of five, two studies were post hoc analysis of clinical trials, two studies were retrospective analyses of patient databases and one study was registry based prospective longitudinal study. We did not identify any randomised controlled trials. One study involved adult participants with diagnosis of interstitial lung disease and data from IPF patients was included in this review. Table 1 describes the characteristics of the included studies.

Risk of bias

The overall risk of bias of five included studies was moderate to serious. (Table 2) Two studies [15,30] were post-hoc analysis of pooled datasets from clinical trials, limiting study population to those who meet eligible criteria for clinical trials [13,14,31] and two studies [32,33] were national registry-based studies which inherently carry a risk of coding error and missing data [34]. One study's entry criteria [33] limited the study population to oxygen dependent patients, who are likely to have advanced disease, registered in Swedevox, Swedish registry for long-term oxygen therapy. In this study, data on diagnostic criteria for IPF was absent, with estimated 80 per cent of probable IPF. Most studies lack information on duration and compliance with statin therapy. Two post-hoc analysis studies used multiple outcome measures with possible outcome reporting bias.

All-cause mortality

Of five included studies, three studies reported the adjusted all-cause mortality and one study reported the adjusted survival. One study reported that statin use was associated with reduced adjusted all-cause mortality (HR 0.76; 95% CI 0.62-0.93)[35]. However, three remaining study did not show association between statin therapy and all-cause mortality or survival [15,32,33].

In the fixed effect meta-analysis, statin use was associated with a reduction in mortality (RR 0.8; 95% CI

0.72-0.99), but there was moderate heterogeneity between studies (I^2=46%). (Figure 2) However, this meta-analysis was dominated by the results of one positive study (Vedel-Krogh 2015), and if we used a random effects model that distributed the weights more evenly, there was no longer any significant association between statin use and all-cause mortality (RR 0.87; 95% CI 0.68-1.12). (Figure 3)

IPF-related mortality

The adjusted hazard ratio for IPF-related mortality was reported in one post-hoc analysis study which suggested that statin use at baseline significantly reduced chance of IPF-related death (HR 0.36; 95% CI 0.14-0.95, p=0.0393)[15].

Decline in pulmonary function

There was no statistically significant association between statin use and decline in FVC % predicted in two post-hoc studies [15,30]. Two studies reported on a composite measure of FVC decline of >10% or death. Meta-analysis did not demonstrate any significant relationship between statin use and the composite outcome. (Figure 4)

Others

One study [15] explored the association with hospital admission and showed no statistically significant difference in all-cause hospital admission between baseline station uses and non-users. However, the difference was statistically significant when adjusted for age, sex, pulmonary function, breathlessness, smoking status, and cardiovascular risk factors and medical history (HR 0.58; 95% CI 0.35-0.84, p=0.0289). Baseline statin user had statistically significant reduction in respiratory related hospital admission than non-users.

Another post-hoc study reported no statistically difference in time to first acute exacerbation of IPF and change in St George's respiratory questionnaire total score between statin user and non-user at baseline [30].

Discussion

This review did not find a consistent relationship between statin therapy and all-cause mortality or decline in pulmonary function in IPF population. A small number of studies were identified, and all studies were observational studies or post-hoc analysis studies, inherently carrying issues with missing data and selection bias. The meta-analysis was dominated by one large study that reported beneficial effects of statins, whereas other smaller studies did not always show similar benefits. We also found limited data suggesting that statins may have a possible effect in reducing hospital admissions. Furthermore, healthy user bias may have contributed to the findings in observational studies, with possible overestimation of the effect of preventative treatment such as statin therapy [33,36]. Of five, four studies reported the prevalence of cardiovascular disease. The prevalence of cardiovascular disease was more common (up to 83%) in statin user compared with non-users (up to 49%).

One limitation of this review is that we focused our search on published scientific literatures and did not screen grey literature as it has not gone through the full peer review. This is because we recognize that the full use of the most recent risk of bias tools such as ROBINS-I requires very explicit and comprehensive reporting of the primary research study. Additionally, we excluded studies written in non-English language, limiting our findings. Among included studies, only two studies reported the prevalence of hyperlipidaemia. None of the included studies reported on values of serum cholesterol and triglycerides. Only one study reported IPF-related death and the causes of death was missing in the majority of studies.

One study checked for statin prescription at two different time points to ascertain continuous statin use, however, there was no information on dosage and adherence. None of the studies collected data on adherence to statin therapy. Sub-optimal adherence to statin therapy has been reported in previous studies [37,38], and this may have resulted in an under-estimate of statin effects in the studies we included. In clinical practice, low-dose statins (e.g. atorvastatin 10mg) are used for primary cardiovascular disease prevention and hyperlipidaemia treatment, and high-dose (e.g. atorvastatin 80mg) is prescribed for secondary prevention following cardiovascular events. A previous study showed that high dose statin therapy resulted in a greater reduction in atherosclerotic plaque inflammation on positron emission tomography-computed tomographic imaging (PET-CT), suggesting dose-dependent anti-inflammatory effect of statin [39]. Different indications for the use of statin therapy and dosage could be potential

confounding factors.

Cardiovascular disease is common in people with IPF [40], and occult cardiovascular disease is also prevalent [41]. Study of COPD and ILD patients, containing 89% IPF patients, undergoing lung transplant evaluation with coronary angiography revealed that 63% of ILD patients had angiographically proven coronary artery disease but only 20% had established diagnosis of coronary artery disease prior to angiography[41]. This suggests that large proportion of IPF patients have hidden cardiovascular disease which could be a potential confounding factor in assessing disease modifying effect of statin in IPF.

Statin is often used in conjunction with other medications for cardiovascular disease prevention. Kreuter et al. (2019) reported on the effect of pairwise combinations of drugs on diseases progression in the ASCEND and CAPACITY trials. Multivariable regression based on a multiple pairs of drugs (e.g. statins and diabetic medications, statins and anticoagulants) did not yield any consistent evidence of beneficial effect when statins were used concomitantly with other drugs[42].

Statin exposure was defined differently in each study. Statin exposure was defined as statin use at starting long-term oxygen therapy in one study and at the clinic visit where the diagnosis of IPF was made in another study. Only one study used presence of two prescriptions within 6 months before and two year before the ILD diagnosis. Other definitions of statin exposure including statin use after the diagnosis of ILD was excluded. The remaining two studies, post hoc from clinical trials, defined exposure as statin use at baseline. Observational cohort studies in pharmacoepidemiology are vulnerable to bias including selection bias and misclassification bias [43]. Therefore, future studies should be conducted under a robust study design.

Reviewing the available literature on the effect of statin in people with IPF showed that there is insufficient evidence to support a full randomised controlled trial. However, emerging evidence from in vitro studies are promising and support antifibrotic effect of statins. In animal study, simultaneous treatment with pravastatin and protein kinase C (PKC) inhibitor exerted synergistic antifibrotic effect in hepatic fibrosis model through statin-induced activated hepatic stellate cell apoptosis [44]. PKC is a family of serine-threonine kinase, which is involved in various signalling pathways including TGFß1-mediated collagen synthesis in pulmonary fibrosis [45], and inhibition of PKC was associated with attenuated ventricular fibrosis following myocardial infarction [46]. Pirfenidone showed dose-dependent inhibitory effect on PDGF-induced PKC activity in hepatic fibrosis model [47]. Additionally, simvastatin inhibited TGF-ß

mediated Smad-3 signalling pathways which play important roles in fibrogenesis [48]. The synergistic effect of statins and pirfenidone may be worth further evaluation.

Conclusion

There is currently insufficient evidence to conclude the effect of statin therapy on disease-related outcomes in idiopathic pulmonary fibrosis. Considering the limitations of available literature, we would recommend a prospective cohort study with capture of dosage and preparation of statin, statin adherence and use of concurrent antifibrotic treatment.

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Declarations of interest: none

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Table 1. Characteristics of the included studies

Author, year	Study population	Design	Intervention	Control	Outcome	
Nadrous, 2004	IPF	Retrospective	Statin n=35	No statin n=442	Mean survival	HR 0.97; 95% CI 0.62-1.52 (p=0.985)
Vedel-Krogh, 2015	IPF Danish Registry	Retrospective	Statin n=261	No statin n=522	All-cause mortality	HR 0.76; 95% CI 0.62-0.93
Ekstrom, 2016	O2 dependent IPF Swedevox registry	Perspective cohort study	Statin n=122	No statin n=340	All-cause mortality	HR 1.13; 95% CI 0.81-1.57
Kreuter, 2017	CAPACITY & ASCEND placebo arm	Post-hoc analysis	Statin n=276	No statin n=348	IPF related mortality	HR 0.36; 95% CI 0.14-0.95 (p=0.0393)
					All-cause mortality	HR 0.54; 95% CI 0.24-1.21 (p=0.1369)
					Decline in absolute FVC> 10%	HR 0.81; 95% CI 0.447-1.40 (p=0.4533)
					All-cause hospital admission	HR 0.58; 95% CI 0.35-0.94 (p=0.0289)

					Resp related hospital admission	HR 0.44; 95% CI 0.25-0.80 (p=0.0063)
Kreuter, 2018	INPULSIS	Post-hoc analysis	Statin n=312	No statin n=749	Annual decline in FVC	Mean difference 50.8ml/yr; 95% CI –10.9 to 112.5 (p=0.1065)
					Time to 1st acute exacerbation	HR 0.76; 95% CI 0.33-1.73 (p=0.5144)
					Change in SGRQ total score	Mean difference 1.22; 95% CI –1.65 to 4.09 (p=0.4039)
					Unadjusted Death statins (n=19) vs. no statin (n=28)	RR 1.63; 95% CI 0.92 - 2.87

	Risk of bias pre-intervention and at intervention			Risk of bias post-intervention domain				
Author, year	**Bias due to confounding**	**Bias in selection of participants into the study**	**Bias in classification of intervention**	**Bias due to deviation from intended intervention**	**Bias due to missing data**	**Bias in measurement of outcomes**	**Bias in selection of the reported result**	**Overall Assessment of bias**
Nadrous, 2004	Moderate	Low	Low	Moderate	Low	Low	Low	Moderate
Vedel-Krogh, 2015	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Ekstrom, 2016	Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate
Kreuter, 2017	Moderate	Moderate	Low	Moderate	Moderate	Low	Serious	Serious
Kreuter, 2018	Moderate	Moderate	Low	Moderate	Moderate	Low	Serious	Serious

Table 2. Risk of bias assessment of included studies

Appendix 1

Medline search terms

1. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
2. HMG-CoA Reductase Inhibitor*
3. HMG CoA Reductase Inhibitor*
4. Hydroxymethylglutaryl-CoA Inhibitor*
5. Hydroxymethylglutaryl-Coenzyme A Inhibitor*
6. Statin*
7. (fluvastatin or rosuvastatin or simvastatin or atorvastatin or pravastatin or lovastatin or pitavastatin)

1 or 2 or 3 or 4 or 5 or 6 or 7

Combined with

1. exp Lung Diseases, Interstitial/
2. (idiopathic interstitial pneumonias or IIP)
3. fibrosing alveolitis
4. (usual interstitial pneumonia or UIP)
5. (Pulmonary Fibrosis or lung fibrosis)
6. Idiopathic Pulmonary Fibrosis or IPF
7. interstitial pneumonia/ or usual interstitial pneumonia
8. Cryptogenic fibrosing alveolitis
9. (fibrotic NSIP or fibrotic lung disease or fibrotic non-specific interstitial pneumoni* or fibrotic non specific interstitial pneumoni*)
10. ((idiopathic and pulmon* and fibro*) or idiopathic fibrotic)
11. (cryptogen* and fibros* and alveolit*)
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11