Lipid-lowering drug therapies and chronic obstructive pulmonary disease: lung failure or just heart failure?

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COPD and atherosclerosis share many risk factors so statins may improve lung function by improving cardiac function.

Introduction

Lipids are intimately involved in metabolism in the lung. Lipid-lowering drugs, primarily statins, are prescribed for patients both with established and with developing cardiovascular disease (CVD) (1). Statins improve microvascular and endothelial function (1,2). As statins inhibit early in the pathway of cholesterol synthesis, they also reduce isoprenoid intermediates involved in the control of protein prenylation and rho kinase, which modulate inflammation (1,2). Statins have been suggested as potential treatments for lung diseases including acute lung injury (3), pneumonia (4), pulmonary fibrosis, pulmonary hypertension (5) and for chronic obstructive pulmonary disease (6). Most studies have suggested benefits in lung disease, but some studies of statins in interstitial lung disease showed adverse effects, although these have not been reproduced recently in a large cohort study (7). The most common clinical situations where lipid-lowering drug therapy is likely to be used are in patients with asthma and/or chronic obstructive pulmonary disease (COPD). The question addressed in this review is whether these drugs contribute anything to the management of common lung diseases as well as of CVD risk factors in the general population.

Search strategy

This review was based on searches of PubMed databases for studies using the terms statin, fibrate and niacin (including individual drug names), as well as asthma (statin, n = 63), chronic obstructive airways disease (statin, n = 102), lung (statin, n = 582) and of clinical trial databases using similar search terms in English from 1980 to 2013. Systematic reviews of statins in asthma and COPD were also abstracted in detail for papers not in PubMed.

Lipoprotein metabolism and the lung

The role of lipoproteins in lung metabolism is underestimated (8). Both LDL receptors and SR-B1 (the principal HDL receptor) are found in lung tissue and phospholipids are the source of fatty acids and other lipid-related moieties required for surfactant production. The Niemann-Pick C lysosomal pathway is involved in cholesterol homeostasis and surfactant production in lung alveolar cells (9). Serum cholestenoic acid and 27-hydroxy-cholesterol [whose production is regulated by a farnesoid-X receptor (FXR)-controlled pathway in the liver] have been suggested to be plasma markers of lung lipid metabolism and to relate to the degree of pulmonary alveolar proteinosis (10). Excess cholesterol impairs surfactant function through changes in surface chemistry (11). Macrophages are a key component of alveoli and are profoundly affected by cholesterol analogous to the effects seen in atheroma formation. Thus, proteins involved in cholesterol or oxidised lipid transport such as the export transporters ABC-A1 and ABC-G1, the scavenger receptors for cholesterol, fatty acids and sterols (SR-B1; CD36; SR-AI/2) located on macrophages are also involved in lung biology (8). Activation of macrophages and the changes induced in macrophage lipid metabolism and receptor expression also occur secondary to infective stimuli, e.g. lipopoly-saccharide (LPS). Mice deficient in apolipoprotein (apo) A-1, the key structural protein of HDL, show increased airway resistance, inflammation and alveolar fibrosis (12). The apoE-deficient mouse model of atherosclerosis has impaired macrophage cholesterol export, but also shows abnormal alveolar development and increased airway resistance (13). ABC-A1-deficient mice (homologous to human Tangier
Corticosteroids activate indoleamine 2,3-dioxygenase (IDO) activity through increased IL-10 secretion acting through glucocorticoid-induced TNF receptor ligand, activation of p52 and the non-canonical NFκB pathway.
The control of dioxygenases is often related to PPAR mechanisms and leukotrienes are one of the group of fatty acids ligands for these receptors (38). An 8-week trial of 10 mg simvastatin in 50 patients showed that statin therapy allied to budesonide reduced sputum eosinophils counts and increased IL-10 and IDO activities (37). A further RCT in 71 smokers using the same statin dose and inhaled steroids showed no difference in FEV1 though an improvement in quality of life scores (39). In a small RCT in 12 patients, simvastatin 40 mg did not show any corticosteroid-sparing effect in eosinophilic asthma, although when patients were completely weaned off steroids, those receiving statins had lower symptom scores, better lung function and a reduced sputum eosinophil counts (40).

Summarising these trials, a systematic review in 2012 identified eight small studies: RCTs (Table 1) and two observational studies (41). Statin use was not associated with any consistent improvements in any clinical or respiratory function parameter, but improvements were observed in inflammation markers. The only data not included in the review were the spirometry performed in the Heart Protection Study (HPS). In HPS, FEV1 was similar in both groups (simvastatin 2.06 l vs. 2.05 l for placebo (p = 0.5); as was forced vital capacity (FVC) (2.82 l vs. 2.82 l (p = 0.9) and both were independent of pretreatment cholesterol levels (42). Overall, the studies of statins in asthma are too small and too short-term for conclusions to be drawn.

<table>
<thead>
<tr>
<th>Study first author</th>
<th>Number</th>
<th>Daily Statin dose</th>
<th>Duration (weeks)</th>
<th>End-point</th>
<th>Result</th>
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<tr>
<td><strong>Asthma trials (41)</strong></td>
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<tr>
<td>Braganza (39)</td>
<td>71 smokers</td>
<td>Atorvastatin 40 mg</td>
<td>4</td>
<td>Lung function</td>
<td>Quality of life improved</td>
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<tr>
<td>Maneechotesuwan (37)</td>
<td>47 steroid treated</td>
<td>Simvastatin 10 mg</td>
<td>8</td>
<td>Airway inflammation</td>
<td>Sputum Eosinophils reduced</td>
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<td>Cowan (40)</td>
<td>43 steroid treated</td>
<td>Simvastatin 40 mg</td>
<td>12</td>
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<td>Hothersall (35)</td>
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<td>Sputum macrophages, leukotriene B4 reduced</td>
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<td>Fahimi (36)</td>
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<td>Menzies (34)</td>
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<td>Simvastatin 20/40 mg</td>
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<td><strong>COPD trials (44,52)</strong></td>
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<tr>
<td>Lee (53)</td>
<td>125 Pulmonary hypertension</td>
<td>Pravastatin 40 mg</td>
<td>26</td>
<td>Exercise tolerance time</td>
<td>Improved in statin group compared with baseline</td>
</tr>
</tbody>
</table>

**Statins and COPD**

Chronic obstructive pulmonary disease is a chronic condition usually affecting elderly people involving sometimes an asthmatic component (this is not seen in the majority of patients), frequent infective exacerbations and physiological dysfunction (ventilation-perfusion mismatching) allied to destructive lung disease (43). COPD combines elements of infection and airways disease (asthma), so the discussions of asthma above are relevant to COPD.

**Basic mechanisms pertaining to COPD**

Statins exert several anti-inflammatory effects, which are potentially beneficial to the asthma component of
COPD (see above). Statins also inhibit Th17 cells, which promote neutrophil-driven inflammation and also stimulate the uptake of apoptotic neutrophils by alveolar macrophages (efferocytosis), which is impaired in COPD. Statins also reduce the release of TGF-β from epithelial cells, a growth and remodelling factor potentially involved in small airway fibrosis (22). Animal studies have shown that statins inhibit the development of emphysema following smoke or elastase lung exposure (44).

Clinical studies of statins in COPD

Studies of statins in COPD are based on case-control and cohort designs. Statins were originally reported to reduce rates of sepsis by 85% in a cohort study of 361 patients of whom 82 had received statin therapy (45), but this finding has not been reproduced in larger cohort studies (4). A matched cohort study \((n = 76,232)\) and two case-control studies \((397 influenza and 207 COPD deaths)\) found a reduced OR for influenza/pneumonia death \([OR, 0.60(0.44-0.81)]\) and COPD death \([0.17(0.07-0.42)]\) in the cohort study and improved hazard ratios in patients on statin therapy (46). A study in China of 1584 cases with COPD exacerbations and 5950 matched controls showed that any statin use was associated with a 30% \((12-44)\) decreased risk of COPD exacerbations with a 40% \((19-56)\) reduction seen with current statin use as well as a dose-dependent relationship (47). In a cohort study in Scotland, which included 1017 patients with COPD, use of statins reduced CVD morbidity and mortality in 443 secondary prevention patients by 65% \((13-85)\) after a 0.52 mmol/l reduction in total cholesterol and non-significantly by 16% \((-89 to +73)\) in 1274 primary prevention patients despite a 0.86 mmol/l reduction; far less than would be predicted (48). However, statin therapy was associated with a reduction in all-cause mortality in both primary and secondary prevention cohorts by 42% \((3-65)\) and 39% \((15-57)\) respectively (49). In the Veterans Administration Normative Aging Study, statin usage attenuated the decline in FEV1 \((0.86(0.73-0.99))\) in a cohort study of \(82\) patients with COPD and pulmonary hypertension (53) and used a walking distance end-point that might be affected by statin-mediated improvement in endothelial function (5) rather than reflecting any improvement in COPD. A review of statin studies \((n = 18)\) in community-acquired pneumonia as opposed to COPD found publication bias and a small potential benefit of statin therapy (54).

Systematic reviews of statins in COPD in 2012 identified nine studies (four retrospective cohorts, one nested case-control study of a retrospective cohort, one retrospective cohort and case series, two population-based analyses and one RCT (Table 1) (44,52). All these small studies showed a reduction in COPD exacerbations \((n = 3)\), number of and time to COPD-related intubations \((n = 1)\), improved pulmonary function \((e.g., FEV1 and FVC) (n = 1)\), exercise capacity \((n = 1)\), COPD \((n = 2)\) and all-cause mortality \((n = 3)\) (44,52). The only RCT included 125 patients with COPD and pulmonary hypertension (53) and used a walking distance end-point that might be affected by statin-mediated improvement in endothelial function (5) rather than reflecting any improvement in COPD. A review of statin studies \((n = 18)\) in community-acquired pneumonia as opposed to COPD found publication bias and a small potential benefit of statin therapy (54).

The HPS, which recruited patients at high risk of CVD, was not included in these reviews. In HPS, deaths from COPD were non-significantly reduced \([simvastatin 26 (0.3%) vs. 39 (0.4%) placebo; RR 0.66; p = 0.11]\) but numbers were small. No difference was seen in all combined respiratory deaths and admissions \([simvastatin 811 (7.9%) vs. 820 (8.0%) placebo; RR 0.98; p = 0.7]\), but there was a trend towards a reduction in this end-point for COPD \([88 (0.9%) vs. 110 (1.1%)]; RR 0.79; p = 0.1) (42).

Other lipid-lowering drugs and lung function

Statins are the best known and most universally efficacious of the lipid-lowering drug therapies. They are not the only ones. Although statins primarily lower LDL-C, they can have secondary effects on other lipoprotein pathways. Statins enhance clearance of apoB-100-containing lipoproteins through the LDL \((apoB_{100}/apoE)\) receptor and thus reduce triglyceride-rich lipoproteins (TGRL) in a dose proportional manner. Most statins are mild inhibitors of cholesterol ester transfer protein (CETP) function and they may regulate PPAR-α function through secondary phosphorylation (55); these effects may underlie the small increase in HDL-C seen with statin therapy (55). Thus, if LDL-C reduction is not the mechanism behind the postulated effects of statins on lung function, other lipid-lowering drugs acting on these alternative pathways also have potential roles in lung disease (20).

Triglyceride-modulating drugs

Peroxisomes are present in alveolar cells and are involved in alveolar lipid metabolism (56). Little is known about the relationship of PPAR agonists and lung disease. Fibrates (PPAR-α) agonists and thiazo-lidinediones (PPAR-γ agonist hypoglycaemic therapies) have been used for many years. Fibrates (PPAR-α agonists) also

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have microvascular effects in atheroma-reducing proteinuric and retinopathy in patients with diabetes (57), but no studies have been performed with these drugs in lung disease. Both PPAR-α (58) and PPAR-γ are involved in the control of inflammation (58) and PPAR-α function influences liver-X-receptor function that may be responsible for the anti-inflammatory effects of these drugs. PPAR-γ may be relevant to lung disease given its associations with asthma, hypoxia, lung injury and fibrosis (59-62). Any effects seen in cohort studies may correlate with changes in HDL-C and triglycerides rather than cholesterol in studies of fibrates or pioglitazone in lung disease, although the pioglitazone effect may be confounded (especially in COPD) by its aldosterone-raising effect and consequent fluid retention.

**HDL-modulating drugs**

The functional biology of HDL is extremely complicated (63). It is difficult to measure HDL turnover as, unlike LDL, cholesterol and proteins have profoundly different kinetics; thus, HDL-C levels in plasma are a poor guide to HDL turnover. Reverse cholesterol transport (e.g. functions of ABC-A1 and ABC-G1) is only one component of the activity of HDL particles, which also includes apolipoproteins, which mediate immune function (63-65). ApoA-I is a core component of HDL, whereas apoE is transferred to HDL from TGR5. ApoA-I (e.g. D-4F) and apoE mimetic peptides reduce alveolar eosinophil and neutrophil concentrations and improve cytokine and oxidative stress profiles in mouse models of asthma (66). HDL is known to be a highly effective anti-inflammatory, to contain specific enzymes to degrade lipid epoxides (paraoxonase) and proteins safely able to carry oxidised lipids and LPS (63) all with potential relevance to asthma and COPD.

Fibrates have indirect actions on HDL metabolism, but their prime action is to increase the turnover of TGR5 and thus LDL clearance (67). Niacin has multiple actions on lipid profiles of which the largest component is to raise HDL-C through a decrease in its clearance rate (68). In mouse models of LPS-induced lung injury, niacin reduces lung inflammation markers through an action via NFκB (69). Niacin increases skin dendritic and Langerhans cell production of prostaglandins (D2 more than E2), thromboxane and leukotrienes, which might exacerbate asthma (70). There are no data on niacin and the incidence of asthma in man, although it may be possible to identify a signal if it exists in the 28,000 patient Heart Protection 2-THRIVE study (71). The greatest increase in HDL-C levels is seen with CETP inhibitors. These act to stop particle remodelling through cholesterol and triglyceride transfer and also reduce LDL-C levels. CETP inhibitors promote cholesterol efflux from cells to HDL particles through the ABC-A1 and ABC-G1 pathways. Their effects on lung cell function or physiology are unknown.

**Atherosclerosis, chronic cardiac failure and COPD**

Atherosclerosis and COPD share many risk factors including prior smoking, a male gender predominance, and greater incidence in patients with diabetes or renal disease. The presence and exacerbations in COPD are known to drive progression of atherosclerosis (72,73). In the OMEGA trial of omega-3 fatty acids, postacute myocardial infarction COPD was associated with a 1.77 [1.01-3.10]-fold increase in CVD events (74). Severe airflow limitation (FEV1 < 50% predicted) in COPD was associated with CVD risk factors and CRP levels in 3877 men in the Tromso heart study (75). A New Zealand cohort study of 1687 patients (age 71 years) admitted with COPD included 596 on statin and 1091 not on treatment. Patients prescribed statins were more often men (59% vs. 49%), have CVD (59% vs. 25%), heart failure (48% vs. 25%) or diabetes (35% vs. 12%). In this study, 671 deaths occurred during 4 years and statin use was associated with a 31% (16-42) reduction in mortality after adjustment for CVD risk factors and frusemide use (a crude proxy for the presence of heart failure) (76).

Coronary atherosclerosis is associated with LDL-C-induced endothelial dysfunction, including erectile dysfunction, another marker of CVD (77) as well as left ventricular dysfunction and chronic heart failure (CHF). Deterioration in CHF often occurs secondary to infections as well as predisposing to them. Thus, CHF and COPD could be closely linked. The association of markers of COPD with CHF has been shown in epidemiological studies of CVD. Cases of new-onset CHF were identified in 13,600 patients in the Atherosclerosis Risk in Communities cohort (78). After 15 years of follow-up, 1369 (10%) participants developed CHF. Age- and height-adjusted odds ratios for CHF increased with quartiles of FEV1 with gender, race and smoking. After adjustment for CVD risk factors and height, the hazard ratios for quartile 1 vs. quartile 4 were 3.91(2.40-6.35) for FEV1 in white women, 3.03 (2.12-4.33) for white men, less for African Americans, but all remained significant after adjustment for markers of inflammation. An association with CHF was also seen for reported new diagnoses of COPD, but not for asthma. Similarly, in 3642 patients from the Multi-Ethnic Study of Atherosclerosis where emphysematous damage was measured on thoracic computerised tomography, carotid intima media thickness (cIMT), a known marker of atheroma burden (79), was associated with reduced FEV1 especially in smokers even after adjustment for CVD risk factors and inflammation (80). Ankle-brachial index (a marker of peripheral arterial disease, PAD) was associated with extent of emphysema, but no relation
was found with coronary artery calcium scores. In a subgroup analysis of 253 patients with COPD from the Rotterdam cohort study (all aged > 55 years), the presence of COPD was associated with a twofold increase in the prevalence of carotid artery thickening (cIMT > 2.5 mm) and the presence of lipid-rich plaque on magnetic resonance imaging (81).

Atherosclerosis affects multiple vascular beds and thus patients with PAD almost always have coronary atherosclerosis. In a study including 3371 patients with PAD, the presence of COPD was associated with an increased risk of both lung and extra-pulmonary cancer mortality (82). Similar data were reported from Japan (83). A cohort study in the Netherlands compared 330 patients with PAD and COPD treated with statins with 480 patients with PAD alone. Statin use was associated with a 52% (0-77) improvement in 30-day survival and a 33% (14-48) improvement in 1-year survival, but only high-dose statin therapy was associated with improved short-term survival (84).

Statins improve coronary and peripheral endothelial function and thus would be expected to improve lung perfusion secondary to larger effects on extracellular fluid volumes through actions on cardiac and renal function. Their direct effects on pulmonary endothelium have been demonstrated in pulmonary hypertension (5), but are less extensive than those induced by inhibition of phosphodiesterase-5 or endothelin-1. The presence of subclinical left ventricular dysfunction or CHF could be a significant comorbidity that is the real target of statin therapy in COPD with predictable improvements in endothelial function and other surrogate markers (5) such as the 6-min walk distance by analogy with studies in pulmonary hypertension and one trial in COPD trial (53). Coronary artery disease, left ventricular hypertrophy (with added risk of ischaemia) and inflammation may contribute to raised troponins in COPD (85,86). Fourfold elevations in troponins are routinely found in COPD exacerbations (86,87). Many patients with COPD show evidence of left ventricular dysfunction including elevations in N-terminal B-type natriuretic peptide (BNP) and troponins (86,88). The only systematic data from a large CVD prevention statin study is that collected in HPS where statin therapy was associated with a small non-significant decrease in COPD deaths or admissions. No data have been published on BNP or troponin concentrations from this trial. This may be an indication for trials of statins and renin-angiotensin-modulating therapies in COPD.

Conclusions

There are good theoretical and biochemical reasons why statins should benefit patients with acute and chronic lung dysfunction. Lipids, isoprenoid cholesterol intermediates and dysfunctional macrophages are found in both atherosclerosis and chronic lung disease. It may be possible to identify subtypes of COPD based on airway response, inflammation, biochemical and imaging markers that would respond well to lipid-lowering therapies (89). One recent trial has compared the use of an inflammation-based algorithm to define a subtype of COPD in which to institute statins as well as other therapies in 35 patients. The St George’s respiratory questionnaire score was improved by 14 vs. 3.5 points (p < 0.001) with parallel improvements in quality of life scores (90). Small scale but highly specific studies using imaging technologies may also be used to investigate the role of lipid-lowering therapies on the progression of COPD (91). However, currently in COPD, clinical studies of lipid-lowering therapies remain small, cohort studies inadequate and randomised control trials vastly underpowered to detect any significant clinical effects (2). Well-designed surrogate marker studies and large-scale clinical trials on clinical pulmonary end-points are still required to identify whether statins or other lipid-lowering drugs have a role in the treatment of lung disease.

The basic biochemical mechanisms of how lipid-lowering drugs affect lung cell function may be clinically irrelevant. The meta-analyses of small-scale trials show little effect for statins to date and there are no data for any other lipid-lowering drugs. The interesting link between inflammation and infection and destabilisation of atherosclerotic plaque may also occur in exacerbations of asthma and COPD with their increases in plasma cytokines and immune cell activation. Thus, the actions of statin in preventing plaque destabilisation and secondary cardiac insufficiency may explain their epidemiological association with better outcomes in asthma and COPD. Despite these associations, statins, beta-blockers and acute coronary intervention are underused in patients with COPD despite the high rate of occurrence of CVD risk factors in this population (92).

Disclosure

None.
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