Rosuvastatin treatment in stable chronic obstructive pulmonary disease (RODEO): a randomized controlled trial

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Abstract. Neukamm A, Høiseth AD, Einvik G, Lehmann S, Høgve T-A, Søyseth V, Omland T (Akershus University Hospital, Lørenskog; Center for Heart Failure Research and KG Jebsen Cardiac Research Centre, University of Oslo, Oslo; Akershus University Hospital, Lørenskog; Haukeland University Hospital, Bergen; University of Bergen, Bergen; Akershus University Hospital, Lørenskog, Norway). Rosuvastatin treatment in stable chronic obstructive pulmonary disease (RODEO): a randomized controlled trial. J Intern Med 2015; 278: 59–67.

Objectives. The objective of this study was to examine whether statin therapy is associated with enhanced endothelium-dependent vascular function, improved pulmonary function and reduced systemic inflammation in patients with chronic obstructive pulmonary disease (COPD).

Design and setting. This randomized, placebo-controlled, double-blind, parallel trial including patients with COPD was performed at two University hospitals in Norway.

Subjects, intervention and measurements. Patients with stable COPD (n = 99) were assigned randomly to receive rosuvastatin 10 mg (n = 49) or matching placebo (n = 50) once daily for 12 weeks. The primary outcome measure was change in endothelium-dependent vascular function measured using peripheral arterial tonometry and expressed as the reactive hyperaemia index. Secondary end-points were change in pulmonary function, as assessed by forced expiratory volume in 1 s (FEV1) and FEV1/forced vital capacity (FVC), and change in the circulating levels of the inflammatory markers interleukin-6 (IL6) and high-sensitivity C-reactive protein (hsCRP).

Results. In the overall study population, no significant between-group difference in change in endothelium-dependent vascular or pulmonary function was observed. Rosuvastatin therapy was associated with a reduction in hsCRP (−20% vs. 11%, P = 0.017) and an attenuation of the rise in IL6 concentration (8% vs. 30%, P = 0.028) compared with placebo. In a prespecified subgroup analysis of patients with a supra-median circulating hsCRP concentration (>1.7 mg L−1), rosuvastatin was associated with improved endothelium-dependent vascular function (13% vs. 2%, P = 0.026).

Conclusions. In stable COPD patients without the standard indications for statin therapy, rosuvastatin treatment is associated with a significant attenuation of systemic inflammation and improvement in endothelial-dependent vascular function in patients with evidence of systemic inflammation.

Keywords: chronic obstructive pulmonary disease, endothelial function, hydroxymethylglutaryl-CoA reductase inhibitors, inflammation, pulmonary disease, randomized controlled trial.

Introduction

During the past few years, it has become increasingly recognized that chronic obstructive pulmonary disease (COPD) is a systemic disorder characterized not only by pulmonary but also by systemic inflammation [1, 2]. The important pathophysiological role of comorbidities in the morbidity and increased mortality associated with COPD has also recently become clear. It has been proposed that the systemic inflammatory component is a link between COPD and its comorbidities,
including cardiovascular disease (CVD) [3, 4]. Low-grade inflammation is commonly associated with increased oxidative stress in the vascular wall, the subsequent reduced bioavailability of endothelium-derived nitric oxide (NO) and impaired endothelium-dependent vasodilator function, an initiating event in the atherosclerotic process [5].

Hydroxymethylglutaryl-CoA reductase inhibitors, commonly known as statins, have documented effects on mortality and morbidity in patients with established coronary artery disease (CAD), but have also been found to reduce the incidence of cardiovascular events in high-risk individuals in the general population [6–8]. It has been proposed that statins exert important effects on the immune system that are independent of the effect on lipids (i.e. pleiotropic effects) [9]. Anti-inflammatory actions contribute to the beneficial cardiovascular effects, but controversy remains regarding the existence and impact of noncardiovascular effects of statins. In retrospective observational studies, statin therapy has been associated with improved survival in patients with COPD [10, 11]. Experimental data also suggest that statins may have beneficial effects on airway inflammation, matrix metalloproteinase activity and mucin production [12–14]. Thus, it remains unclear whether statins exert their potential beneficial effects in COPD by primarily affecting vascular or respiratory function, and whether or not such beneficial effects are mediated by attenuation of systemic inflammation.

To address these questions, we conducted a randomized, placebo-controlled, double-blind trial to test the hypothesis that treatment with rosuvastatin in patients with stable COPD is associated with (i) enhanced peripheral endothelium-dependent vascular function, (ii) improved pulmonary function and (iii) attenuation of systemic inflammation, as expressed by decreased levels of circulating inflammatory markers. Furthermore, we prospectively hypothesized that the beneficial effect of rosuvastatin may be particularly pronounced in patients with evidence of increased systemic inflammation.

Materials and methods

Trial design

Effect of ROSuvastatin therapy on peripheral vasodilator function, inflammatory markers and pulmonary function in patients with stable chronic Obstructive pulmonary disease (RODOE; clinicaltrials.gov number NCT00929734; EudraCT number 2009-011659-35) was a randomized, placebo-controlled, double-blind, parallel-group clinical trial.

Participants

Consecutive patients referred to the pulmonology outpatient clinics of two university hospitals in Norway with a verified diagnosis of COPD were eligible for participation. Exclusion criteria included history of or active CAD, cerebrovascular or peripheral vascular disease, and diabetes mellitus (Table S1).

Intervention

After initial investigation, all patients were randomly assigned to either rosuvastatin 10 mg or matching placebo once daily for 12 weeks.

Measurements

All patients completed a questionnaire about comorbidities (Charlson comorbidity index), respiratory symptoms according to the Modified Medical Research Council (MMRC) dyspnoea scale [15] and smoking habits. Spirometry was performed with reversibility testing using salbutamol as recommended by Miller et al. [16]. A 6-min walk test was conducted according to the guidelines of the American Thoracic Society [17]. Smoking was expressed as current smoking (yes/no) and number of pack-years. Arterial and venous blood samples were collected after an overnight fast during which patients abstained from smoking. The concentration of high-sensitivity C-reactive protein (hsCRP) was measured with the Cobas c501/502 system (Roche, Mannheim, Germany), and interleukin-6 (IL6) concentration was measured with the Cobas e602 system (Roche).

Endothelial function

Endothelium-dependent vascular function was assessed by peripheral arterial tonometry (PAT) using the EndoPAT device (Itamar Medical, Caesarea, Israel). This method has been shown to correlate closely with the vasodilator response of coronary vessels following infusion of the endothelium-dependent vasodilator acetylcholine [18] and to provide prognostic information concerning the future incidence of cardiovascular events in the general population [19, 20].
Study end-points

The primary end-point was the change from baseline in digital endothelium-dependent vascular function, expressed as reactive hyperaemia index (RHI) measured by PAT. Secondary end-points were the changes from baseline in postbronchodilator forced expiratory volume in 1 s (FEV1), FEV1/forced vital capacity (FVC) and levels of hsCRP and IL6. Tertiary end-points included change in MMRC dyspnoea scale and 6-min walking distance (6-MWD). The difference in the changes between treatment groups was used as the effect measure.

Statistical analyses

Baseline characteristics of the study population were summarized within each group. The difference in the changes between the rosuvastatin and placebo groups from baseline to 12 weeks for primary and secondary end-points and feasibility measures was estimated using analysis of covariance (ANCOVA). In accordance with the prespecified analysis plan, we evaluated treatment effects in subgroups with elevated circulating pro-inflammatory markers, defined as levels of hsCRP or IL6 above the median value. We also performed two post hoc sensitivity analyses, first excluding patients with increased CVD risk according to the Adult Treatment Panel III (ATP-III) criteria and secondly excluding those with a history of asthma. All statistical analyses were performed using SPSS STATISTICS (Version 20; IBM Corporation, New York, NY, USA and SASR (Version 9.2; SAS Institute, Inc., Cary, NC, USA) software.

The study was conducted in compliance with good clinical practice (GCP) regulatory requirements and with approval from independent ethics committees in accordance with the Declaration of Helsinki. Informed written consent was obtained from all participants. Further details of the methods used are available in the Appendix S1.

Results

Baseline data

Complete data were available at the end of the study for 94 of the 99 patients enrolled (Fig. 1). Table 1 presents demographic and baseline characteristics of patients in each group. In the overall population, the mean (±SEM) age was 65 (±0.6) years, 48% were women, the mean body mass index was 24 (±0.4) kg m⁻², the mean number of pack-years of smoking was 38 (±1.6), mean FEV1 was 1.4 (±0.06) L and mean FEV1/FVC was 47% (±1.3). Overall, 25% of patients had a history of hypertension, and 23% had a history of bronchial asthma (Table 1). None of the patients had a previous diagnosis of heart failure.

Primary, secondary and tertiary outcome measures

In the complete-case analysis (n = 94), there was no significant change in endothelium-dependent vascular function, expressed as the RHI, in either the treatment group or the placebo group. Moreover, there was no significant difference in the primary outcome measure (i.e. the change in RHI) between the groups (Table 2 and Fig. 2).

The relative change in endothelial function, defined as change in RHI, was 6.65% [95% confidence interval (CI) 1.80% to 15.11%] in the rosuvastatin group and −1.27% (95% CI −8.33% to 5.79%) in the placebo group (P = 0.292). In a secondary, predefined, multivariate regression analysis adjusting for covariates with possible impact on endothelial function (history of hypertension, gender and current smoking status), treatment with rosuvastatin was not significantly associated with change in RHI (P = 0.157). However, in a prespecified subgroup analysis of patients with supra-median hsCRP concentrations (i.e. >1.7 mg L⁻¹), rosuvastatin therapy was associated with a significant between-group difference in change in endothelium-dependent vascular function (13% vs. 2%, P = 0.026;
A similar trend was observed in patients with supra-median IL6 concentrations (i.e. >3.7 pg mL\(^{-1}\)) (7% vs. 2%, \(P = 0.131\)). With regard to the secondary outcome measure of change in markers of systemic inflammation, rosuvastatin therapy was associated with a significant reduction in hsCRP level (20% vs. 11%, \(P = 0.017\)) and a significant attenuation of the rise in the level of IL6 (8% vs. 30%, \(P = 0.028\)) compared with placebo. By contrast, there were no significant between-group differences in change in the spirometry values FEV1 (L), FEV1 (% of predicted) and FEV1/FVC (\(P = 0.462\), \(P = 0.344\) and \(P = 0.292\), respectively; Table 2). Moreover, there was no difference in the changes in the tertiary measures of symptoms of dyspnoea according to the MMRC dyspnoea scale and 6-MWD (data not shown). Both imputation and per-protocol analyses yielded the same results as the complete-case analysis, and sensitivity analyses yielded the same conclusion regarding the effect on endothelial function. Of the 94 patients who completed the RODEO trial, 86 met the criteria for low CVD risk. Amongst these 86 patients, the effect on endothelial function (expressed as RHI) remained significant (\(P = 0.032\)) in the subgroup of patients with signs of elevated baseline inflammation defined as hsCRP >1.7 mg L\(^{-1}\) (\(n = 43\)). 72 patients who completed the study had no previous diagnosis of asthma. In the subgroup of patients without a history of asthma but with elevated baseline inflammation (\(n = 37\)), there was a significant effect on endothelial function (\(P = 0.048\)) as well as a significant difference in the change in concentration of the inflammatory markers hsCRP and IL6 (\(P = 0.006\) and \(P = 0.035\), respectively).

### Feasibility data

Treatment compliance was confirmed by a significant lipid-lowering effect of rosuvastatin. Compared
with placebo, rosuvastatin administration caused significant decreases in plasma total and LDL cholesterol levels by 24% and 41%, respectively. HDL cholesterol increased by 7%, and serum triglyceride levels decreased by 11%.

Safety end-points
Rosuvastatin was generally well tolerated by all patients. Possible side effects were reported by a total of 12 (26%) patients in the rosuvastatin group and 21 (43%) in the placebo group. The most frequent adverse events reported were constipation, diarrhoea, nausea and acute exacerbation of COPD. There was a nonsignificant trend towards more frequent exacerbations during the treatment period in the placebo group (27% vs. 15% in the rosuvastatin group, \( P = 0.160 \)). There was no significant between-group difference in the change in alanine transaminase and creatine kinase levels (Table S2). The reported serious adverse events were mainly acute exacerbations requiring hospitalization during the treatment period [\( n = 4 \) (9%) in the rosuvastatin group and \( n = 3 \) (6%) in the placebo group]. There were no suspected unexpected serious adverse reactions during the treatment period (Table S3).

Discussion
Main study results
The main finding of the present investigator-initiated, randomized, placebo-controlled, double-blind

Table 2 Change in end-points between treatment groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rosuvastatin (n = 47)</th>
<th>Placebo (n = 47)</th>
<th>( P )-value\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>RHI</td>
<td>2.47 (0.10)</td>
<td>2.54 (0.10)</td>
<td>2.65 (0.10)</td>
</tr>
<tr>
<td>lnRHI</td>
<td>0.87 (0.04)</td>
<td>0.90 (0.04)</td>
<td>0.94 (0.04)</td>
</tr>
<tr>
<td>FEV1, L</td>
<td>1.34 (0.09)</td>
<td>1.35 (0.08)</td>
<td>1.47 (0.10)</td>
</tr>
<tr>
<td>FEV1, %</td>
<td>48.3 (2.77)</td>
<td>49.3 (2.75)</td>
<td>52.1 (2.75)</td>
</tr>
<tr>
<td>FEV1/FVC, %</td>
<td>46.9 (2.01)</td>
<td>47.3 (1.87)</td>
<td>48.8 (1.72)</td>
</tr>
<tr>
<td>hsCRP, mg L(^{-1})</td>
<td>1.4 (0.8, 3.7)</td>
<td>1.2 (0.7, 2.6)</td>
<td>1.8 (1.0, 4.4)</td>
</tr>
<tr>
<td>IL6, pg mL(^{-1})</td>
<td>4.1 (2.9, 5.2)</td>
<td>4.1 (3.4, 5.5)</td>
<td>3.4 (2.7, 4.7)</td>
</tr>
</tbody>
</table>

Continuous data are presented as mean (SEM). Biomarker data are presented as median (25th, 75th percentile). FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; hsCRP, high-sensitivity C-reactive protein; IL6, interleukin-6; RHI, reactive hyperaemia index.

\textsuperscript{a}ANOVA.

\textsuperscript{b} \( P < 0.05 \) paired \( t \)-test.

\textsuperscript{c} \( P < 0.05 \) Student’s \( t \)-test.

Fig. 2 Reactive hyperaemia index (RHI) and SEM in all patients (\( n = 94 \)).

Fig. 3 Reactive hyperaemia index (RHI) and SEM in patients with high-sensitivity C-reactive protein concentration above the median value (\( n = 47 \)).
clinical trial is that short-term rosuvastatin treatment does not improve either endothelial function or lung function in patients with stable COPD without a history of CVD and diabetes, but significantly attenuates systemic inflammation. Notably, in a prespecified subgroup analysis of patients with hsCRP concentration >1.7 mg L⁻¹, rosuvastatin treatment was associated with improved endothelium-dependent vascular function, compared with placebo. Given that systemic inflammation is associated with the frequency of exacerbations [21] and outcome in COPD [22, 23] and that endothelium-dependent vascular function is believed to reflect vascular health and the risk of atherosclerotic disease, these findings are compatible with the theory that long-term treatment with statins may improve COPD outcome in patients with stable disease with elevated hsCRP concentrations. Although no effect of statins on the incidence of COPD exacerbations was observed in a recently reported large-scale clinical trial, there might nevertheless be an effect on the incidence of cardiovascular events in patients with evidence of elevated baseline inflammation.

Rationale for randomized trials of statin therapy in COPD

Although the results of several retrospective observational trials suggest a beneficial effect of statin therapy on survival in patients with COPD [10, 24], the underlying mechanisms remain unclear. To date, the results from three randomized controlled trials on statin treatment amongst patients with COPD have been published. The first study included 125 patients with stable COPD and reported a beneficial effect of statin treatment on exercise time; the effect was most prominent amongst patients with decreasing concentrations of inflammatory markers during treatment [25]. The second study, which included 56 patients, failed to demonstrate any significant effect of statins on circulating inflammatory markers [26]. Accordingly, there has been an urgent need for randomized clinical trials to elucidate the potential pathophysiological mechanisms of COPD and to assess the efficacy and safety of statin therapy in patients with stable disease. This was the rationale for conducting the RODEO trial. Very recently, the findings of the third study were published [Simvastatin for the prevention of exacerbations in moderate-to-severe COPD (STATCOPE)]. In this multicentre trial, no effect of statin treatment on the incidence of COPD exacerbations was observed, but subgroups of COPD patients with different levels of inflammation were not evaluated and the study was not powered to assess the effect on cardiovascular events [27].

Effect of rosuvastatin treatment in stable COPD

It has previously been shown that statin treatment exerts anti-inflammatory effects in different patient groups, including patients with CVD, diabetes or rheumatoid arthritis [28–31], and the large-scale Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial extended these findings to individuals with elevated hsCRP levels without hyperlipidaemia [8]. The beneficial effect of statin therapy appeared to be consistent across a wide range of cardiovascular end-points and subgroups. However, as JUPITER included a high proportion of obese patients, the characteristics of the participants may not be representative of a population with stable COPD, and therefore, the results cannot be extrapolated to this population. Moreover, two previously reported clinical trials in patients with COPD have demonstrated inconsistent results [25, 26].

It has previously been shown that hsCRP and IL6 levels are elevated amongst patients with COPD, and this is associated with unfavourable outcomes [22, 32, 33]. The observed slight increase in the levels of inflammatory markers might reflect disease progression in the placebo group, as we observed a nonsignificant trend towards increased exacerbations in this group. Inflammation did not correlate with current smoking in our population, and correction for smoking status did not change the results in a multivariate model. In addition, patients also abstained from smoking for at least 12 h before biomarker measurements, as mentioned above.

In a recent prospective case–control study, statin use was associated with improved survival amongst patients with COPD; this association was dependent on the level of systemic inflammation [24]. COPD patients with evidence of chronic low-grade inflammation may therefore represent a subgroup that could potentially benefit from statin treatment. The current results demonstrate that statin therapy attenuates systemic inflammation and suggest that targeting patients with increased levels of hsCRP may identify those who may benefit most from statin therapy in terms of improvement in vascular function. Because
patients with COPD are at increased risk of cardiovascular events and measurement of vascular reactivity has been shown previously to provide additional prognostic information to conventional risk markers in patient groups without known CVD, vascular reactivity assessment seems to represent a valid although imperfect surrogate marker of atherosclerotic events. We believe that long-term randomized multicentre trials including at least 3000 patients with a 3-year follow-up will be required to accurately define the beneficial effect of statin therapy in stable patients with COPD and to evaluate whether the observed statin effect on endothelial function in patients with evidence of increased systemic inflammation would also translate into reduced incidence of cardiovascular end-points.

There are several possible explanations for the apparent lack of effect of rosuvastatin on indices of pulmonary function observed in the current study, including insufficient duration of therapy, drug dose or statistical power. However, the effects observed on blood lipids, inflammatory markers and vascular function suggest that the lack of effect on pulmonary function may be real and that the beneficial effects of statins in stable patients with COPD may preferentially target the cardiovascular system. This theory is supported by the current finding of a lack of effect on the dyspnoea scale and exercise capacity measures in our study, as well by the recently published results of the STATCOPE trial.

Strengths and limitations

The strengths of the study include the randomized, placebo-controlled design, the well-characterized study population and the use of well established and reproducible methods to assess changes in vascular function, pulmonary function and inflammatory activity. The low percentage of patients who withdrew from the study and the high acceptability of the study drug represent further strengths.

However, there are several study limitations, including the short duration of treatment and the relatively small sample size. The generalizability of our results depends on the representativeness of the study population. We included an equal number of men and women, and we believe the age range is representative of a typical population with COPD. However, the study population was ethnically homogenous (all Caucasian), and the results may not be generalizable to a non-Caucasian population. Baseline values of RHI in this selected population of patients with COPD were generally within the normal range. This may also have contributed to the failure to document a beneficial effect of statin therapy in the overall study population. We limited inclusion to patients without a clear indication for statins based on comorbidities. As the beneficial effect of statin therapy in patients with CAD and diabetes mellitus is well established [34], patients with a history of these diseases were not eligible for the present study. In addition, we showed robust results in the sensitivity analysis excluding patients at high CVD risk according to the ATP-III criteria. It is considered that patients with COPD without these comorbidities are still at increased CVD risk [35].

Conclusion

Short-term treatment with rosuvastatin in patients with stable COPD without known CVD was associated with reduced systemic inflammation and resulted in improved endothelium-dependent vascular function in the subgroup of individuals with supra-median concentrations or hs-CRP at baseline. These findings suggest that (i) the beneficial effect of statin therapy in stable COPD patients may be confined to those with evidence of systemic inflammation and (ii) measurement of hsCRP levels might be useful as part of a personalized medicine strategy to identify this patient group.

Conflict of interest statement

TO received grants, personal fees and nonfinancial support from Abbott Laboratories, personal fees from Siemens Healthcare, grants, personal fees and nonfinancial support from AstraZeneca, and personal fees from Roche Diagnostics. AN has received a speaker fee from AstraZeneca. All other authors have no conflict of interests to declare.

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**Authors’ contributions**

AN, study design, data collection and analysis and drafting of the first version of the manuscript; ADH, data collection, data analysis and manuscript preparation; GE, data analysis and manuscript preparation; T-AH, biochemical analyses and manuscript preparation; SL, data collection and manuscript preparation; VS, study conception and design and manuscript preparation; TO, study conception and design, data interpretation and manuscript preparation.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Methods.

Table S1. Exclusion criteria.

Table S2. Acceptability and feasibility measures.

Table S3. Safety endpoints.

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