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Use of rosuvastatin in HIV-associated chronic obstructive pulmonary disease: A randomized pilot study

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Abstract

Objectives—Chronic obstructive pulmonary disease (COPD) is more prevalent in HIV-infected individuals and is associated with persistent inflammation. Therapies unique to HIV are lacking. We performed a pilot study of the HMG Co-A reductase inhibitor rosuvastatin to determine effects on lung function.

Design—Randomized, placebo-controlled, triple-blinded trial.

Methods—HIV-infected individuals with abnormal lung function were recruited from an ongoing lung function study. Participants were randomized to 24 weeks of placebo (n=11) or rosuvastatin (n=11) using an adaptive randomization based on change in peripheral C-reactive protein levels at 30 days of treatment. Forced expiratory volume in one second (FEV_1) and diffusing capacity for carbon monoxide (DLco) %-predicted were compared to baseline at 24 weeks in the two groups using Wilcoxon rank-sum. %-predicted change at 24 weeks in pulmonary function variables was compared between groups using simulated randomization tests.

Results—The placebo group experienced a significant decline in FEV_1%-predicted (p=0.027), and no change in DLco%-predicted over 24 weeks. In contrast, FEV_1%-predicted remained stable in the rosuvastatin group, and DLco%-predicted increased significantly (p=0.027). There was no significant difference in absolute change in either measure between placebo and rosuvastatin groups.

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Conclusion—In a pilot study, use of rosuvastatin for 24 weeks appeared to slow worsening of airflow obstruction and to improve DLco in HIV-infected individuals with abnormal lung function, although comparison of absolute changes between the groups did not reach significance. This study is the first to test a therapy for COPD in an HIV-infected population, and large-scale clinical trials are needed.

Keywords

HIV; lung; statin; inflammation; chronic obstructive pulmonary disease

Introduction

Chronic obstructive pulmonary disease (COPD) is common in HIV-infected individuals and accounts for an increasing proportion of mortality [1]. HIV-associated COPD encompasses several phenotypes of lung impairment [2–5]. Global Initiative for Chronic Obstructive Lung Disease (GOLD)-defined COPD (based on airway obstruction) [6] is found in approximately 15–20% of HIV-infected individuals and is related to smoking [2, 7, 8]. Impairments in diffusing capacity for carbon monoxide (DLco) are also prevalent in HIV-infected populations, reported in up to 64% of individuals, and seen in both smokers and non-smokers [2, 8, 9]. Both phenotypes are associated with local and systemic inflammation even in ART-treated individuals [10, 11].

Standard COPD treatments such as inhaled corticosteroids may have significant side effects in HIV [12–15], and specific therapeutic interventions to improve pulmonary outcomes in HIV are lacking. Even smoking cessation is not an absolute solution as lung function may continue to decline after quitting, and we see impairment in HIV-infected non-smokers [10]. Several factors distinguish COPD in the HIV-infected population including early age of onset and a relationship between lung function and HIV viral load [2, 4, 8, 10], suggesting novel therapies are needed to prevent and treat HIV-associated COPD.

3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have have pleiotropic effects that target common pathways to end-organ damage and are an attractive potential intervention for diseases secondary to inflammatory processes including COPD. They are potent systemic immune modulators and may have direct effects on the lungs [16–19]. In the HIV-uninfected COPD population, trials of statins have produced conflicting results [20–22]. How results of these trials apply to HIV-infected individuals, who may have unique mechanisms leading to COPD including a heightened inflammatory response and immune activation, is unclear.

We performed a pilot study of rosuvastatin in HIV-infected individuals with COPD defined either by abnormal spirometry or an abnormal DLco to determine feasibility, establish infrastructure for a larger, multi-center study, and assess impact on pulmonary function variables.

Methods

Trial Design

The study was a prospective, adaptive response, double-blinded, placebo-controlled randomized pilot study. Institutional review boards at all sites approved the studies. Participants signed written informed consent. The study was registered at clinicaltrials.gov (NCT01881971).

Participants

Subjects with documented HIV infection were enrolled from our ongoing cohort [2, 8–10] or from local HIV pulmonary clinics. Additional inclusion criteria included age 18–80 years, forced expiratory volume in one second/forced vital capacity (FEV_1/FVC)<0.70 and/or DLco<80 %-predicted, and not currently on lipid-lowering therapy. Participants could be stably on or off ART and needed to have a stable smoking status.

Screening procedure

Subjects underwent history/physical examination and measurements of fasting lipids, renal and liver function, creatinine kinase, hemoglobin A1C and fasting glucose. Individuals were excluded if they met clinical criteria for statin use [23] or other exclusion criteria (Supplemental Content).

Interventions

The intervention group received 10 mg of rosuvastatin daily for 24 weeks unless they were Asian or currently receiving ritonavir, in which case they received 5 mg daily. The placebo group received a similar tablet. Medications were prepared and dispensed in a blinded fashion by the University of Pittsburgh Investigational Drug Service.

Assignment to treatment group

Subjects were randomly assigned to rosuvastatin or placebo using a drop-the-loser response-adaptive design [24](Supplemental Content).

Study protocol

Pulmonary function testing, chest CT scan, and research blood sampling were performed at baseline. Subjects were then randomized to rosuvastatin or placebo by the data coordinating center who informed the Investigational Drug Service. At week 4, participants returned for clinical blood work and hsCRP to update the adaptive randomization. Pulmonary function testing was repeated at weeks 12 and 24. Chest CT was repeated at week 24. St. George's Respiratory Questionnaire [25] was administered at baseline and weeks 4, 12, and 24.

Primary endpoint

The primary outcome variable was difference between treatment groups in the 24-week change of post-bronchodilator FEV_1 %-predicted.

Secondary endpoints

Secondary endpoints included decline in other pulmonary function measures as well as change from baseline to 24 weeks in the rosuvastatin group versus the placebo group. Changes in other measures such as lipids, hsCRP, percentage of CT emphysema, St. George's Respiratory Questionnaire, inflammatory biomarkers, and peripheral blood mononuclear cell (PBMC) gene expression were also examined and are reported in Supplemental Content.

Study procedures

Pulmonary function—Pre- and post-bronchodilator spirometry and measurement of DLco were performed per American Thoracic Society standards [26, 27](Supplemental Content).

Chest computed tomography—Non-contrasted CT scans of the chest were acquired per protocol (Supplemental Content).

Biomarkers and PBMC gene expression—Biomarker levels and gene expression were measured in serum and PBMCs (Supplemental Content).

Statistical methods

This pilot study was designed to explore feasibility of the intervention and establish infrastructure for a larger, multi-center trial (Supplemental Content). Simulations were used to compare observed values in each treatment group to the simulated null distribution (Supplemental Content). In addition to comparison across treatment groups, we analyzed within treatment group change of key outcome variables to determine if they significantly differed from zero. When conditioning on treatment group, the signed-rank test was used.

Results

Participant flow and recruitment

We screened 436 participants in our research registry to determine if they met pulmonary function criteria for study entry (details in Supplemental Digital Content, Methods and Supplemental Figure 1).

Baseline data

Participants in each treatment group were comparable (Table 1). Median age was 50.3 years and 32% were female. Spirometry demonstrated median post-bronchodilator FEV_1 of 83%-predicted and diffusion impairment was common with a median DLco value of 64% predicted (Supplemental Table 1).

Outcomes

Pulmonary variables—Median change in FEV_1%-predicted from baseline to 24 weeks was −2.3% overall with an absolute decrease of 75 ml. In the placebo group, FEV_1 %-predicted declined significantly at 24 weeks compared to baseline (median change = −4.5%,

p=0.027, Supplemental Figure 2). In contrast, FEV_1 remained stable over 24 weeks in the rosuvastatin group (median change = −0.3%, p=0.92). Comparison of the change in the placebo and rosuvastatin groups at 24 weeks was not significantly different (p=0.25). Similar changes were seen for FVC. For DLco%-predicted, there was no significant change from baseline to 24 weeks in the placebo group (median change = 3.2%, p=0.32, Supplemental Figure 2), but there was a significant increase in the rosuvastatin group (median change = 6.7%, p=0.027). Change in %-predicted for the placebo and statin groups was not significantly different (p=0.38).

Discussion

Lung disease is prevalent in HIV-infected individuals and associated with morbidity and mortality. This pilot study demonstrated that participants randomized to rosuvastatin had no significant decline in FEV_1 %-predicted over 24 weeks in contrast to those in the placebo group who experienced a significant decline, although comparison of rate of change between the groups was not significant. We also saw improvements in DLco, a major lung abnormality in HIV-infected individuals for which there are no tested therapies [2, 5, 8, 9]. This study is the first investigation of a COPD treatment specifically in HIV-infected individuals, and we hypothesized that statin therapy in HIV-infected individuals could decrease inflammation, thereby slowing the progression of pulmonary abnormalities.

Despite the current prevalence of lung function abnormalities and COPD in HIV-infected individuals, no interventions have been specifically tested in HIV-infected populations. Although HIV-associated COPD shares common features with COPD in the HIV-uninfected population, it also has unique features that suggest that different treatments may be needed. For example, lung function abnormalities consistent with COPD can be seen in never smokers [2, 10]; and data support a role of the virus in COPD development or progression [4, 28]. Interactions of standard COPD treatments such as inhaled corticosteroids with protease inhibitors and potential for inhaled corticosteroids to increase bacterial pneumonia and tuberculosis risk also point to a need for therapies tailored to HIV-infected individuals.

HMG-CoA reductase inhibitors have been proposed as potential therapies for COPD in the HIV-uninfected population. Despite the promising theoretical framework supporting statin use for COPD, trials in the HIV-uninfected population have been conflicting [29]. The STATCOPE trial, a large, randomized trial, failed to show benefit of simvastatin use in decreasing COPD exacerbations [20]. This study also did not see a significant decrease in rate of decline in FEV_1, although the statin group had a somewhat smaller decrease in FEV_1. A smaller randomized study of rosuvastatin found no change in pulmonary function in stable COPD patients over 12 weeks, but did report decreases in CRP and attenuated increase in IL-6 [30].

In HIV-infected individuals, increased and alternative pathways of inflammation, including monocyte activation and endothelial dysfunction, explain differences from the HIV-uninfected population. Impact of statin use on the monocyte activation marker sCD14 and the endothelial dysfunction marker endothelin-1 in this pilot study lends support to this hypothesis. The relatively preserved FEV_1 in our population may also explain differences in

our findings from previous COPD trials that enrolled individuals with more advanced disease that may be less amenable to intervention.

Interestingly, many participants had normal spirometry, but an abnormal DLco. An impaired DLco is the most common pulmonary function abnormality in HIV [2, 8, 9], but there are no current therapeutic agents targeting DLco. Our trial is the first investigation of this class of drugs in DLco impairment. Although DLco may reflect multiple physiologic measures, it is most strongly associated with airway obstruction, emphysema, and inflammation in HIV-infected populations [2, 8, 9]. Statins may influence DLco by decreasing alveolar cellular inflammation, by beneficial effects on the vascular endothelium, or by effects on cardiac function. In addition, despite the fact that many participants with an abnormal DLco did not have accompanying evidence of clinical airway obstruction, rosuvastatin still appeared to prevent decline in FEV_1%-predicted. This effect on FEV_1 decline in mild obstruction or clinically normal spirometry also supports the idea that statin treatment could be used as a preventive therapy in this at-risk population.

Our study has several limitations. First, it was a pilot study designed to explore feasibility and establish infrastructure for a larger, multi-center trial. Although we saw differences in rate of decline within the treatment groups, we were not powered to detect differences between groups, and larger studies are needed before statins could be recommended for clinical use for this indication. We also enrolled individuals with pulmonary function deficits, many whom were current or former smokers. Whether statin use would impact individuals with normal pulmonary function to slow development of COPD is unknown. In addition, the intervention lasted only 24 weeks and effects may change over a longer time-period. We do not know if a higher dose or a different statin might have had a greater effect on pulmonary function. Because this study included only a small sample, the results may not be generalizable. Our trial did include individuals with a range of lung function who were predominantly smokers, similar to other HIV-infected populations [4, 7].

This pilot study is the first trial of an intervention for COPD in HIV-infected individuals and demonstrates slowing in decline in FEV_1 over 24 weeks. The study is also the first to test effects of therapy on DLco, an important COPD phenotype in HIV-infected individuals. A larger-scale study based on lung function outcomes and stratified by smoking status is needed to determine if statins should be prescribed for HIV-infected individuals with COPD, but these results suggest a therapeutic option unique to HIV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline demographics for the cohort and by treatment group.

	All (N=22) Median (Q1, Q3) n (%)	Placebo (N=11) Median (Q1, Q3) n (%)	Rosuvastatin (N=11) Median (Q1, Q3) n (%)
Age (years)	50.3 (47.1, 53.2)	49.2 (48.5, 52.9)	51.3 (45, 54.4)
Female, n (%)	7 (31.8)	3 (27.3)	4 (36.4)
African-American, n (%)	12 (54.5)	6 (54.5)	6 (54.5)
Hispanic, n (%)	1 (4.5)	1 (9.1)	0 (0)
Body mass index (kg/m^2)	24.5 (20.9, 27.6)	25.7 (21.3, 26.6)	21.7 (20.6, 27.9)
Ever smoked cigarettes, n (%)	19 (86.4)	10 (90.9)	9 (81.8)
Total pack years smoked	12.1 (4.8, 27.4)	11.7 (10, 20.9)	13 (4, 27.1)
CD4 cell count (cells/μl)	630 (526, 784)	660 (539.5, 866)	624 (505.5, 756.5)
HIV viral level < 40 copies/ml, n (%)	17 (77.3)	9 (81.8)	8 (72.7)
ART use, n (%)	21 (95.5)	11 (100)	10 (90.9)
hs-CRP (mg/l)	0.27 (0.13, 0.6)	0.18 (0.1, 0.37)	0.40 (0.17, 1.07)
Total cholesterol (mg/dl)	164 (148, 204.3)	160 (144.5, 175.5)	176 (157.5, 209)
HDL (mg/dl)	45 (36.3, 66.5)	41 (36.5, 58.5)	47 (36.5, 72.5)
Total cholesterol/HDL	3.7 (2.5, 4.8)	3.7 (3.4, 4.2)	4.7 (2.2, 5.2)
LDL (mg/dl)	89 (69, 105)	89 (81, 98.5)	101.5 (69, 133.5)

Abbreviations: ART, antiretroviral therapy; hs-CRP, high sensitivity C-reactive protein; HDL, high density lipoprotein; LDL, low density lipoprotein; SD, standard deviation; Q, quartile.