[ONLINE SUPPLEMENTAL MATERIAL]

Statin Use and Asthma Control in Patients with Severe Asthma

Amir A. Zeki[1a,1b,4,5,] Justin Oldham[1a], Machelle Wilson[2], Olga Fortenko[1a], Vishal Goyal[1a], Michael Last[2], Andrew Last[3], Ayan Patel[4], Jerold A. Last[1a,1b,5], Nicholas J. Kenyon[1a,1b,,4,5].

[1a]Department of Internal Medicine. [1b]Division of Pulmonary, Critical Care Medicine, and Sleep Medicine.

[2]Department of Public Health Sciences. Division of Biostatistics.

[3]Department of Obstetrics & Gynecology.

[4]Clinical and Translational Science Center.

[5]Center for Comparative Respiratory Biology & Medicine.

MATERIALS AND METHODS

Study Design

The UCAN is staffed by three pulmonologists with expertise in severe asthma, and two registered respiratory therapists (RRT). The RRTs see all patients at every clinic visit and perform in-clinic spirometry, collect ACT scores, perform routine history and physical examinations, and maintain a secure, online database that includes clinical data on all patients in UCAN. During each clinic visit, symptoms, medication use including rescue bronchodilator use, in-clinic spirometry, PEFR, exacerbations (yes/no, number, type [ED visit, hospital admission, unplanned/urgent clinic visit, etc.]), and physical activity limitations were determined and recorded in the medical chart.

All UCAN patients receive a written Asthma Action Plan to fortify their initial and continuous asthma education by both asthma physicians and our RTTs. The plan includes regular and logged home PEFR measurements, and instructions on when to use oral corticosteroids, with direct contact information of our RRTs and UCAN clinic.

Study Subjects

In general, all patients who are seen in UCAN must have a clinical diagnosis of asthma, as defined by the following: FEV_1 <80% and FEV_1/FVC ratio <80% with evidence of reversible airflow obstruction and/or as diagnosed by a pulmonary asthma specialist. If not present, patients must demonstrate PEFR variation of >20%, and/or evidence of airway hyperresponsiveness/hyperreactivity (AHR) as defined by a positive methacholine (MCh) bronchial challenge test. Reversible airflow obstruction was confirmed by an increase of 200 mL *and* 12% change in FEV_1 or FVC post-bronchodilator inhalation, and/or a positive MCh bronchial challenge. Atopic status was determined by measuring blood immunoglobulin E (IgE) levels and RAST panel.

For this study, all patients selected were on daily moderate or high-dose ICS, and had daily asthma symptoms most days of the week (>3 times/week), required additional controller therapy in addition to daily ICS (e.g. LABA, LTRA, etc), had persistent airflow obstruction (FEV_1 <80% predicted), at least one urgent care visit per year, and required more than 2 to 3 corticosteroid bursts per year (Table 1).

Data Collection Procedures

The inclusion criteria for each subject included a confirmation of asthma diagnosis by the pulmonary attending asthma sub-specialty physicians in the UCAN clinic. For those meeting inclusion criteria, at least two qualified visits per year during the study timeframe were evaluated. Investigators chose visits by reviewing the first and last visit of each year the patient was seen in the UCAN clinic during the study timeframe. A visit was deemed qualified if it met the above criteria. If a visit was not qualified the investigator examined the next visit if evaluating the first visit of the year, or the second-to-last visit if evaluating the last visit of the year. This method was reiterated until at least two qualified visits were found for that particular year. The number of clinic visits varied from as low as two visits per year per patient, to as high as 26 visits over five years for one patient. Most clinic visits ranged from 3 to 8 visits per patient over at least two years. This process was repeated for every year the patient was seen in the UCAN clinic during the study timeframe.

For peripheral blood eosinophil counts, patients were screened based on the availability of a complete blood count with differential counts, within three months before or after each clinic visit (e.g. a six-month window surrounding each visit). If there was more than one blood draw that qualified, the lab result closest in time to the clinic visit was used to maximize relevance. Twenty-three of the 31 statin-users (74%; the exposure group) had at least one blood draw within this time period as compared to 68 of the 134 non-users (51%; the control group).

Development of Online Integrated Study Database

This project required database integration from three sources of data and then further abstraction of multiple encounter notes from (1) the hospital EMR, (2) pre-existing UCAN Access™ (Microsoft®, Redmond, WA) database, and (3) patient paper charts. The U.C. Davis CTSC Biomedical Informatics program provided the data retrieval, data integration, and electronic data capture services required for this study.

Data were first compiled for subjects previously enrolled in the UCAN clinic utilizing our pre-established online Access™ database. This database provided the start date of when subjects were enrolled into UCAN clinic and all other baseline measurements such as spirometry results, symptoms, medication information, etc.

These data were supplemented with EMR encounter notes and patient paper chart records to fill gaps in data acquisition. All of these data were then integrated and imported into a new password-secured online Access™ database developed specifically for this study, which provided virtual forms to capture all data abstracted from the aforementioned three sources. The database was backed-up automatically online every 24 hours to assure data integrity and security.

This was a novel approach utilized by our CTSC Biomedical Informatics staff to solve the problem of divergent datasets, which was necessary to assure efficient data retrieval, data integrity, easy multi-user interface, and readily downloadable datasets into Excel™ (Microsoft®, Redmond, WA) in a format accessible for immediate statistical analysis.

Asthma Exacerbations

We examined the rate of severe exacerbations measured as the number of exacerbations per month at each patient encounter. The same rules of model selection applied to this variable as described in the main text of the manuscript. Our definition of 'severe exacerbation' included any one of or combination of the following: unplanned/urgent clinic visit, emergency department (ED) visit, hospital admission, and/or respiratory failure requiring endotracheal intubation.

Based on historical experience in our clinic, over the first 12 months of joining the UCAN clinic (502 patients, 77% female), our patients with severe asthma achieved a 92% reduction in urgent clinic visits, 85.3% reduction in ED visits, 97% reduction in hospitalizations, and 96.2% reduction in intubations[2,3]. This is an average reduction in severe exacerbations of over 92% for any given type of exacerbation, resulting in a very low incidence of acute asthma exacerbations (< 8%) in our UCAN population.

Statistical Analysis

Summary Statistics and Epidemiology

To obtain summary statistics for the various covariates of interest, variables measured at each encounter (i.e. multiple encounters per patient) were averaged across encounters to obtain one value per

variable for each patient (Table 1). This provides an average value for continuous variables and the proportion of encounters where the variable occurred (e.g. patient answered 'yes') for categorical variables. For example, if WBC was measured at more than one encounter, the average across encounters was calculated for each patient, yielding the average WBC for each patient. For categorical variables, such as smoking, if the patient never smoked then the value across encounters would be zero. However, if the patient smoked at half of her encounters then her value for the smoking variable would be 0.5. For the continuous variables, the averages reported for statin-users or non-users were then averaged across patients in each group. For the categorical variables, the averages reported for each group are the average proportion of 'yes' responses for the statin-users versus statin non-users. Values with a p-value <0.05 were considered statistically significant.

Independent t-tests were performed for average FEV_1, FVC, $FEF_{25-75\%}$, PEFR, *FEV_1% predicted*, BMI, ACT, absolute eosinophils, percent eosinophils, WBC, age, and weight. The Kruskal-Wallis test was performed for the proportion of encounters for smoking history, nocturnal symptoms, corticosteroid burst, ICS, LABA, systemic steroid use, montelukast, 5-LO inhibitor, albuterol, ipratropium, omalizumab, aspirin, NSAID, PPI or H_2 blocker. Chi Square or Fisher's exact tests were performed for sex, ethnicity, GERD, sinusitis, rhinosinusitis, allergic syndrome, diabetes, CAD, and HPL.

Model Selection

The problem of missing data was beyond the scope of this investigation, as the state of the art is evolving, but will be considered in future research involving the imputation of missing data for categorical data. We did not correct for missing data or attempt imputation solutions. This remains a known limitation and potential confounder in observational studies of this kind.

RESULTS

Cohort Characteristics

Significant (at the 0.1 level) differences were found between statin-users and non-users in the following variables: FEV_1, FVC, $FEF_{25-75\%}$, *FEV_1% predicted*, PEFR, age, montelukast, ipratropium, aspirin, PPI/H_2-blocker, sex, GERD, sinusitis, diabetes mellitus, CAD, and HPL. In addition to these variables, ethnicity, obesity (defined as BMI>30 kg/m^2), and current or past smoking were included during model selection. For each endpoint and each covariate, the p-value at removal was determined (data not shown). The parameter estimates and their standard errors (or means and their standard deviations) for the significant variables for each endpoint at final model fitting are shown in Table 1.

Some conditions rare to this study cohort were not listed or compared between statin-users and non-users given their low prevalence in our study population. Among non-users: hemophilia A, hepatitis C, deep venous thrombosis, lupus, breast cancer, HIV, Crohn's disease, Sjogren's disease, endometrial cancer, essential thrombocytopenia, goiter, osteoporosis, meningioma, aspirin sensitivity, fibromyalgia, atrial fibrillation, mitral valve prolapse, ascending aortic aneurysm. Among statin-users: Cushing's syndrome, diverticulitis, cholelithiasis, hypothyroidism, and Parkinson's disease.

Asthma Exacerbations

We also evaluated whether or not statin-use was associated with reduced or increased acute asthma exacerbations per month. There was a trend (p=0.071) towards a very small increase in the rate of severe exacerbations among statin-users (0.01 ± 0.054 exacerbations per month). This equates to 1 exacerbation in 100 months or 8.3 years, an extremely low event rate of unclear clinical significance. The final statistical model indicated that severe exacerbations were predicted by three variables, namely age (p=0.028), smoking history (p=0.021), and ethnicity (p=0.0052). Specifically, older age was associated with a small decrease in severe exacerbations, smoking history predicted a higher rate of severe exacerbations, and ethnicity predicted a higher rate of severe exacerbations (African Americans (p=0.096), Asians including Indians/Pakistanis (p=0.0074)). There were no significant interactions amongst significant variables. The final model accounted

for all expected and identified confounders (Table 1) including steroid use (ICS and systemic), smoking history, *FEV_1% predicted*, obesity, ethnicity, age, FVC, aspirin use, and co-morbidities such as CAD, HPL, DM, GERD, and sinusitis.

Lung Function

Statin-users compared to non-users had an increase of 0.036 ± 0.06 liters in FEV_1 (p=0.56), 0.026 ± 0.18 liters in FVC (p=0.88), 0.088 ± 0.16 liters in $FEF_{25-75\%}$ (p=0.59). Conversely, for the lung function parameter PEFR, statin-use was associated with a decrease of 26.8 ± 25.7 L/min compared to statin non-users (p=0.92) (Table 2).

The final model showed that FEV_1 was predicted by three variables: age, *FEV_1% predicted*, and FVC. Increasing age was associated with a decrease in FEV_1 (p<0.0001), and both higher *FEV_1% predicted* and higher FVC were associated with higher FEV_1 (p<0.0001 for both comparisons). Each 1 liter increase in FVC was associated with a 0.63 ± 0.02 liter increase in FEV_1. There were no significant interactions amongst all significant variables in the model.

In the final model, age and ethnicity alone predicted FVC, where increasing age was associated with a decrease in FVC (p<0.0001), and ethnicity was associated with increased FVC in white, African American, and Asian patients, but decreased FVC in Hispanic patients (p<0.0001). There were no significant interactions amongst significant variables.

In the final model, four variables predicted $FEF_{25-75\%}$ lung function: age, *FEV_1% predicted*, FVC, and montelukast use. Increasing age was associated with decreased $FEF_{25-75\%}$ (p=0.0012), both higher *FEV_1% predicted* and higher FVC were associated with higher $FEF_{25-75\%}$ (p<0.0001 for both parameters), and montelukast use was associated with higher $FEF_{25-75\%}$ by 0.14 ± 0.07 liters (p=0.046). For each 1 liter increase in FVC, there was a 0.37 ± 0.06 L increase in $FEF_{25-75\%}$. There were no significant interactions amongst significant variables.

In the final model, three variables predicted PEFR: systemic steroid use, PPI or H_2-blocker use, and FVC. Systemic steroid use was associated with a reduction of 45.8 ± 13.9 L/min in PEFR (p=0.0012), whereas PPI or H_2-blocker use was associated with an increase of 7.7 ± 12.3 L/min in PEFR (p=0.0044) and each 1 liter increase in FVC was associated with an increase of 67.7 ± 7.3 L/min in PEFR (p<0.0001). There was a significant interaction between statin-use and PPI/H_2-blocker use (p=0.023). Among statin-users and non-users alike, concomitant PPI/H_2-blocker use was associated with an increase in PEFR, from 322.8 to 387.9 L/min in statin-users, and from 349.6 to 357.3 L/min in non-users, respectively.

Symptoms

Statin-users had a lower risk (odds ratio of 0.93, p=0.84) of needing an oral corticosteroid burst compared to non-users. Patients taking statins tended to use albuterol and ipratropium inhalers less often than non-users (odds ratios of 0.46 (p=0.41) and 0.83 (p=0.71), respectively). Statin-users had a higher probability of manifesting limited physical activity and nocturnal symptoms/awakenings (odds ratios 1.09 (p=0.91) and 1.71 (p=0.39), respectively) (Table 2).

In the final model (Table 2), corticosteroid burst was best predicted by *FEV_1% predicted*, smoking history, and diabetes mellitus. Increased *FEV_1% predicted* was associated with a reduced need for steroid burst (p=0.021), while smoking history and diabetes mellitus were associated with an increased need for steroid burst (p=0.046 and 0.0056, respectively). There were no significant interactions amongst these significant variables.

Age, smoking history, and FVC predicted ipratropium use. Ipratropium use increased with increasing age (p=0.0069) and smoking history (p=0.034), while it decreased with increasing FVC (p=0.0095). There were no significant interactions amongst significant variables.

In the final model, limited physical activity was best predicted by aspirin use and higher FVC, both of which were associated with less physical activity limitations (p-values of 0.035 and 0.016, respectively). No significant interactions were noted. For nocturnal symptoms, the final model showed that obesity alone

predicted the increase in nocturnal symptoms/awakenings (p=0.042), without any significant interactions with other variables.

Peripheral Blood Counts

Statin-use was associated with an insignificant reduction in the total white blood cell count (WBC) of 0.77 ± 0.72 (p=0.29), a slight increase in peripheral blood absolute eosinophil counts (0.024 ± 0.06, p=0.68), and small increase in percent eosinophils (0.28 ± 0.64, p=0.66).

In the final model, systemic steroid use was the only variable that predicted a slight increase in WBC of 1.8 ± 0.65 (p=0.0066), where there were no significant interactions amongst variables. Statin-use was associated with a trend towards a slight increase in peripheral blood absolute eosinophil counts (0.024 ± 0.06, p=0.68), however, the variability was so high that the final model did not identify parameters that could predict the absolute eosinophil count (Table 2). Similarly, statin-use was associated with an insignificant increase in percent eosinophils (0.28 ± 0.64, p=0.66), however, in the final model systemic steroid- and aspirin-use predicted the percent eosinophil count. Systemic steroid use was associated with reduced percent eosinophils by 1.75 ± 0.50 (p=0.0006), and aspirin-use was associated with reduced percent eosinophils by 1.03 ± 0.49 (p=0.039). All values are reported as the estimate ± standard error.

DISCUSSION

Study Limitations

The healthy-user effect must be addressed for a study like this, especially since statin-use was associated with at least one benefit, e.g. higher ACT scores. The healthy-user bias, where statin-users may see the doctor more regularly and be more compliant with treatment, is often difficult to fully account for. Although there were no statistically significant differences in the number of *months observed per patient* between statin-users (18.7) and non-users (15.3) (p=0.09 by Mann-Whitney test), there was a significant difference in the number of *clinic visits per patient* between statin-users (5.7) and non-users (4.1) (p=0.008 by Mann-Whitney test). Statin-users had on average 1.6 more clinic visits per patient than non-users for the period observed. However, the hierarchical mixed effects logistic regression model we used accounted for different numbers of observations or clinic visits (on the subject level). Therefore, as far as these criteria relate to the healthy-user effect, we attempted to correct for this possible phenomenon in our models. Other healthy-user effects beyond this were not measured or accounted for, and this remains a limitation of this study design in general.

REFERENCES

1. Hothersall EJ, Chaudhuri R, McSharry C, *et al.* Effects of atorvastatin added to inhaled corticosteroids on lung function and sputum cell counts in atopic asthma. *Thorax* 2008;63(12):1070–5.

2. Kivler C, Vukovich C, Schinaman, *et al.* Cost savings parallel improved outcomes in severe asthma utilizing respiratory care practitioners. *J Allergy Clin Immunol* 2002;109(Supplement):S314 (Abstract).

3. Kivler C, Vukovich C, Kutler S, *et al.* Cost Savings Parallel Improved Outcomes In Severe Asthma Utilizing Respiratory Care Practitioners. *Am J Resp Crit Care Med* 2003;167:A209 (Abstract).