PROTECTIVE EFFECT OF STATIN USE IN THE PROGRESSION OF DRY TO EXUDATIVE AGE-RELATED MACULAR DEGENERATION

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PROTECTIVE EFFECT OF STATIN USE IN THE PROGRESSION OF DRY TO EXUDATIVE AGE-RELATED MACULAR DEGENERATION

by

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ABSTRACT

Protective Effect of Statin Use in the Progression of Dry to Exudative Age-Related Macular Degeneration

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Purpose: Age-related macular degeneration (ARMD) is a leading cause of irreversible blindness in the industrialized world. Studies suggest that HMG CoA reductase inhibitors (statins) might slow the progression of dry ARMD to the exudative stage. We set out to determine if statin use reduces the risk of progression to exudative ARMD in a matched case-control study.

Methods: An epidemiological study of 61 cases with exudative ARMD matched by age, gender, and race to 61 controls with early, high-risk ARMD determined by prospective ophthalmologic examination.

Results: The risk of exudative ARMD was increased by smoking within the past 20 years (OR=5.8, *95% CI 1.42-23.77*) and reduced by use of statins (OR=0.2, *95% CI 0.04-0.93*). Further, the duration of statin use up to four years was associated with an increasing degree of protection (*9% reduction each month, 95% CI 0.85-0.98*).

Conclusion: Statin use may reduce the progression from dry to exudative ARMD.

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Gregory Nettune, **UT Southwestern Medical Student Research Forum**, Poster presentation, 2005.

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CHAPTER ONE
Introduction

Age-related macular degeneration (ARMD) is a leading cause of irreversible blindness in industrialized countries. ARMD is characterized by the progressive accumulation of subretinal deposits that eventually become clinically apparent as drusen and pigmentary changes in the retinal pigment epithelium. The severity of these features is a major predictor of the risk of developing complications of ARMD including exudation. Recent studies suggest that statins (HMG CoA Reducatase Inhibitors) may prevent exudative complications of ARMD possibly through their beneficial effects on dyslipidemia, anti-inflammatory effects, and anti-angiogenic effects.

The role of statins in preventing exudative complications of ARMD has been suggested by several recent studies. One prospective population-based study found that statin users were nearly four times less likely to have progression of their ARMD than those not using statins, however, this finding did not reach statistical significance.[1] A large nested case-control study by McGwin at a VA hospital revealed that dry ARMD patients were 50% less likely to have filled a statin prescription when compared to non-ARMD patients.[2] This study, however, used hospital codes to determine current statin use and therefore could not accurately measure duration or consistency of statin use. A case series study by Wilson of patients at a VA hospital suggested statin use was associated with a near 50% reduction in risk of developing choroidal neovascular membrane

(CNVM) in early ARMD patients.[3] This study, however, had no control group with which to compare the cases.

A number of studies have addressed the relationships between ocular features, systemic conditions, lifestyle, and diet in development of exudative ARMD. Many studies have shown that smoking increased the risk of developing early ARMD.[4,5,6,7,8] Smoking also increases progression to exudative ARMD and three population based studies show an association of neovascular ARMD with current smoking with estimated odds ratios ranging from 2.5 to 5.6.[9,10,11] A dose-response relationship was also found between smoking and neovascular ARMD.[12] Additional studies have shown omega-3 fatty acid consumption[13] and fish consumption to have a protective effect on patients[14,15] while some studies show no association[16,17] and one showed a negative association[18]. Other studies have suggested a role for fat, fruit, and nut intake, obesity, exercise, and C-reactive protein levels in progression to exudative ARMD.[19,20,21,22,23]

We therefore undertook a case-control study to test the possible effect of statin treatment in preventing the progression of dry to exudative ARMD. We designed our study with prospective diagnosis of ARMD to reduce misclassification bias seen in prior studies, and chose the case-control design because it is efficient for answering questions about rare diseases and those with long incubation periods such as ARMD. We also questioned our subjects directly to confirm statin use history and other risk factor information in the medical records. We also used dry ARMD patients as controls to ensure more a comparable control group to our cases with exudative ARMD.

CHAPTER TWO
Patients, Methods, Results, Discussion

Patients and Methods

Selection of research subjects

Our subject population consisted of 209 Caucasian men and women who visited the Aston Eye Clinic at UT Southwestern Medical Center in Dallas, Texas, at least one time between 1998 and 2004 and had agreed to participate in a study of hereditary eye disease. All subjects underwent a complete ophthalmologic examination by a retina specialist (A.O.E.), who was looking specifically for dry or exudative ARMD. Dry ARMD was defined as the presence of a minimum cumulative drusen area of 393,744 μm^2 (equivalent to an approximately 700 micron diameter circle) and the absence of exudation or geographic atrophy. Exudative ARMD was defined as CNVM in patients with a minimum cumulative drusen area of 393,744 μm^2.

Patients eligible to be cases were the 93 who had been found to have exudative ARMD, while eligible controls were the 116 subjects with early nonexudative dry ARMD. We attempted to match each case patient with the control patient of the same gender with the nearest date of birth but not more than 5 years difference. If two or more eligible controls had the same date of birth, we selected among them using a table of random numbers. Of the 93 potential case patients, 10 were excluded for lack of a matched control within the five year matching age range; 7 died before they could be interviewed; 2 declined to answer the questionnaire; and 13 did not have a working telephone number. This left 61

cases and 61 age- race-gender-matched controls. None of the cases or controls reported a family history of ARMD.

Data Collection

All cases and controls were contacted by telephone by one of the authors, who obtained family history of ARMD; history of smoking including type of tobacco products smoked, number of pack-years smoked, and year last smoked; history of regular fish consumption and the type of fish most often consumed; the number of years of regular statin drug use; and whether they had ever been diagnosed with exudative ARMD and if so, when. The date of onset of exudative ARMD was determined from medical records review and verified by the telephone history. Since exudative ARMD has a rapid onset and causes significant vision loss, the patients' recall of the onset of exudative ARMD and the dates of their first diagnosis generally agreed closely with information in medical records.

Definition of Duration of Statin Use

For the case patients the duration (in months) of statin exposure was the period from beginning date of statin use until the date of onset of exudative ARMD. For the control patients, it was defined as the duration from the beginning of statin use until the date of onset of exudative ARMD of the control's matched case. No subjects reported discontinuous statin use.

Statistical Methods

The association of statin use, age, smoking history, and fish consumption with case-control status was analyzed with conditional logistic regression, a multivariate analytic technique for categorical outcomes that maintains the matching of the design.[24] We used the Logistic procedure of SAS/STAT software (version 9.12, SAS Institute, Cary, NC) with the strata statement.

Evaluation of the distribution of the duration of statin use (Figure 1) identified a highly skewed distribution in which 51 (84%) of the case-control pairs had individual statin use of 4 years duration or less, and 10 (16%) had individual statin use sparsely distributed from 5 to 25 years. Concerned about indication bias in long-term statin use in the elderly[25] and concerned that the sparseness in the distribution beyond 4 years would reduce the power to evaluate the hypothesis, after an initial analysis with all 61 case-control pairs we confined the rest of the analysis to the 51 pairs with statin use of 4 years or less.

We tested for an overall effect of statin use with a dichotomous measure (0 = ver used, 1 = ever used) and for a dose-related effect in two ways: first, with an interval measure of the number of months of statin use, and second, with a three-level ordinal measure (0 = never, 1 = one or two years, 2 = three or four years).

We included age (in years) as a covariate in the analysis because having matched cases and controls within 5 year intervals left some residual age differences that had a small confounding effect. Other covariates that were evaluated for confounding effects were

recent (within 20 years) or remote (more than 20 years ago) history of smoking, pack-years of smoking, amount of fish consumed per month, and usual type of fish consumed (fatty, omega-3 acid-containing fish vs catfish).

The adjusted odds ratio (and its 95% confidence intervals), controlling for all variables in the model, was derived by exponentiating the adjusted logistic regression coefficient (and the coefficient ± 1.96 times its standard error). The adjusted odds ratio was interpreted as an estimator of independent relative risk.[26]

Results

In a conditional logistic regression analysis controlling for age, recent smoking, catfish and omega-3 fatty fish consumption in all 61 case-control pairs, statin use of any duration tended to protect from progression to exudative ARMD (OR = 0.41, 95% CI 0.15-1.11, p = 0.08). In the 51 case-control pairs where statin use did not exceed 4 years, using statins for 4 years or less was significantly associated with an overall 80% reduction in exudative ARMD (OR = 0.21, 95% CI 0.04-0.93, p = 0.04, Table 2); whereas, in the 10 pairs with longer statin use, there was a similar, though nonsignificant, trend toward a reduction in exudative ARMD risk (OR = 0.36, 95% CI 0.03-4.67, p = 0.43). In analysis of case-control pairs with statin use for 4 years or less, each month of statin use was associated with an approximate 9% reduction in conversion to exudative ARMD (OR = 0.91, 95% CI 0.85-0.98, p = 0.01).

Current smoking or previous history of smoking within the past 20 years was associated with an almost 6-fold increase in risk of conversion to exudative ARMD (OR = 5.80,

95% CI 1.42-23.77, p = 0.01); whereas, quitting smoking over 20 years ago tended to carry a reduced risk (OR = 0.41, 95% CI 0.16-1.10, p = 0.08). Regular fish consumption per se was not significantly associated with an increased risk of exudative ARMD (OR=1.89, 95% CI 0.35 – 10.20, p = 0.46), but there were interesting opposite trends for different types of fish usually consumed. Most often consuming fatty fish rich in omega-3 fatty acids tended to show a protective effect (OR = 0.57, 95% CI 0.20-1.58, p = 0.28); whereas, most often consuming catfish, which in Texas is usually deep fried in saturated oils, tended to be associated with an increased risk (OR = 1.96, 95% CI 0.57-.69, p = 0.28).

Discussion

This study reveals that patients with exudative ARMD, when compared to patients with dry ARMD, were 80% less likely to have used statins. This suggests that statins may have a strong inhibitory effect on the progression of dry ARMD to the more disabling exudative form. Our finding appears relatively strong for ARMD patients who took statins for 4 years or less, but because of the sparseness of case-control pairs with statin use for more than 4 years, our study was unable to address the effects of statin use for longer periods. The nonsignificant trend in the latter group suggests that the preventive effect may extend to longterm use, but larger studies are needed to address this question.

This study was the first study of statin use to prevent exudative ARMD which applied a stringent diagnostic definition of macular degeneration while utilizing a case-control design comparing exudative ARMD cases to dry ARMD controls. The design has a

number of strengths. The diagnoses of dry and exudative ARMD in all subjects were based on direct examination for ARMD changes by a retina specialist who applied uniform diagnostic criteria. We used dry macular degeneration patients as controls, which ensured that the controls were comparable to the cases on potential confounding factors. Since exudative ARMD is the most destructive of the forms of ARMD, and since treatment options are limited, it is important to consider prevention as a major treatment modality in dry ARMD patients. Our subjects were better controls than those used in other studies since our controls were patients with macular degeneration and who are the same in most ways to their matched cases and therefore do not introduce bias into the comparison.

The study yielded some initially surprising results regarding smoking and fish consumption. When you looked only at smokers who either currently smoked or who had quit within the past 20 years, there was a strong association with exudative ARMD. Additionally, this group of recent or current smokers showed a dose response effect of increasing risk of exudative ARMD. Therefore, it appears that continued or recent smoking increases the risk of progressing to exudative ARMD. We observed that fish intake was not protective and fish intake per month actually showed a nonsignificant trend towards being a risk factor. This probably reflects the fact that most of our subjects were not eating fish high in omega fatty acids. When we looked at the type of fish that our subjects reported eating most commonly, eating a fish high in omega-3 fatty acid was associated with a protective effect (OR = 0.57) although this was not significant. More cases than controls reported eating catfish as the most commonly eaten fish in their diet. According to the USDA, catfish is one of the fish with the lowest concentration of

omega-3 fats of all the fish mentioned. It contains only 0.2g of omega-3 fatty acids per 3 oz serving.[27] Additionally, in Texas where most of our subjects live, it is nearly always served deep fried. The subjects who reported eating catfish as the most commonly consumed fish had an increased risk of having exudative ARMD (OR=1.96) although this trend was not significant. Since diets high in saturated fats are likely to actually increase the risk of developing exudative ARMD, we recommend that patients with dry ARMD be educated about the types of fish that are protective and the types that are not protective. Simply advising the patient to increase their fish intake can be misleading.

The main limitation of our study was the relatively small sample size of matched case-control pairs and the fact that 10 of the 61 pairs had unusually long statin use that complicated the analysis. Consequently, the main analysis had only 51 pairs with ideally distributed duration of statin use. This sample size, nevertheless, was sufficient to achieve statistically significant results in the evaluation of short term statin use for up to 4 years. A larger sample would have allowed a more robust evaluation of statin use for longer than 4 years and of other important risk factors such as fatty, omega-3 fatty acid-containing fish versus fried catfish. Another limitation was the reliance on self-reported histories of statin use and other risk factors. This was necessary because long term medical records were unavailable for some of the subjects. Statin use and the risk factors we studied are practices with clear-cut beginnings and endings, which are more likely to be remembered accurately than more poorly recalled events such as dietary histories. Finally, this study only enrolled Caucasian subjects as cases and controls and therefore the results may not be applicable to patients of other races. While studies suggest that

ARMD is much more prevalent among Caucasians, future studies may wish to investigate the role of statins in ARMD of non-caucasian patients.

Since a genetic variant in the gene encoding the protein called complement factor H (CFH) was recently identified that increases the risk of developing ARMD several fold, future studies may want to investigate the role of statins is these patients.[28] Additionally, our study used patients who reported no family history of ARMD and therefore they may respond differently to statins than either a patient with family history or a patient with the genetic variant in the gene encoded by CFH. A double masked randomized control trial of statins will be required to fully investigate the role of statins in the progression of ARMD.

Table 1 Characteristics of Subjects*

Demographic Characteristics	Exudative AMD Cases	Early AMD Controls
Mean age in years (SD)	81.4 (7.1)	80.9 (6.7)
Female (%)	31 (61)	31 (61)
Causasian race (%)	51 (100)	51 (100)
Smoking within 20 years (%)	15 (29)	4 (8)
Consumed primarily omega-3 fatty fish† (%)	31 (61)	34 (67)
Consumed primarily catfish‡ (%)	17 (33)	10 (20)
Used statins within 4 years (%)	8 (16)	15 (29)

*Analysis includes the 51 case-control pairs with statin use of 4 years or less.

†Subjects reported that when fish is consumed it is most often a fish high in omega-3 fatty acids (tuna, salmon, herring, sardines, or mackeral).

‡Subjects reported that when fish is consumed it is most often catfish.

Table 2 Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) from conditional logistic regression model of exudative ARMD*

Variables	Adjusted OR (95% CI)	*P* value
Statins used for ≤4 years	0.20 (0.04-0.93)	0.04
Smoked within past 20 years	5.80 (1.42-23.77)	0.01
Age (years)	1.30 (0.85-1.98)	0.22
Omega-3 fatty fish the main fish consumed*	0.57 (0.20-1.58)	0.28
Catfish the main fish consumed	1.96 (0.57-6.68)	0.28

*Analysis includes the 51 case-control pairs with statin use of 4 years or less.

Table 3 Dose-response effects of statin use and recent smoking*

Variables	Adjusted OR† (95%CI)
Duration of statin use	
None‡	1.0
1 to 2 years	0.48 (0.08 - 3.03)
3 to 4 years	0.03 (0.002 - 0.53)
Amount of recent smoking§	
No smoking‡	1.0
≤ 20 pack-years	2.04 (0.22 - 18.78)
21–40 pack-years	8.09 (0.44 - 149.56)
> 40 pack-years	11.37 (0.55 - 236.59)

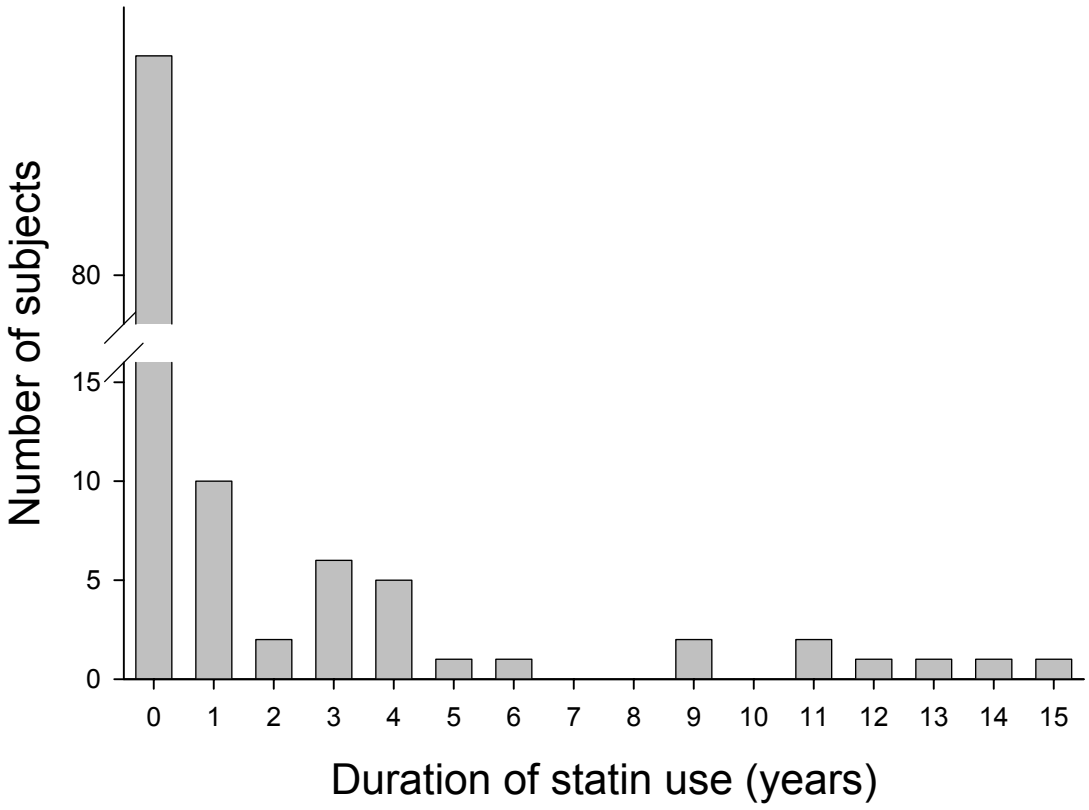
* Analysis includes the 51 case-control pairs with statin use of 4 years or less.

† Adjusted for age, catfish consumption, and fatty fish consumption

‡ Reference category

§ Subjects who stopped smoking >20 years ago are included in the no smoking category.

Figure 1. Distribution of the number of years of statin use by case and control subjects.



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Vitae

EDUCATION

UT SOUTHWESTERN MEDICAL SCHOOL, Dallas, TX — MD anticipated June 2007

DARTMOUTH MEDICAL COLLEGE, Hanover, NH — Masters Degree in Public Health June, 2003

PRINCETON UNIVERSITY, Princeton, NJ — Bachelor of Arts, June 2000

EXPERIENCE

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Developed, administered, analyzed a survey of patient preferences for health care at the White River Junction VA Hospital under the guidance of Dr. William Weeks — Jan 2003 – July 2003

PROGRAM OFFICER — New York, NY
Helen Keller Worldwide –An International Public Health NGO — Nov. '00 – May '02
Assistant to Director of Onchocerciasis Program

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For Graduate Studies in Health Care Quality Improvement

UT SOUTHWESTERN MEDICAL STUDENT RESEARCH FORUM — January 2005
Poster presentation