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ORIGINAL ARTICLE

Anti-Inflammatory Drug Use and Age-Related Macular Degeneration

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ABSTRACT

Purpose. Basic research has shown that early processes in the development of age-related macular degeneration (ARMD) are related to inflammation. The purpose of this manuscript is to evaluate the association of ARMD and the use of anti-inflammatory medications.

Methods. A nested case control study was carried out among male patients at the Veteran's Medical Center in Birmingham, Alabama (BVAMC). Cases were 614 patients with incident ARMD diagnosed between 1997 and 2001 by International Classification of Disease, Ninth Revision code. Controls (4526) were individuals with no diagnosis of ARMD by International Classification of Disease, Ninth Revision coding and matched on age. Formulary records of all medications dispensed through the Veteran's Administration Medical Center were accessed. All oral or injectable drugs with anti-inflammatory properties were considered anti-inflammatory medications for study purposes. Topical ophthalmic and dermatologic preparations were not considered anti-inflammatory.

Results. Among veterans with a diagnosis of ARMD 24% (150/614) patients had filled a prescription for any of the anti-inflammatory medications compared with 60% (3051/4526) individuals in the control population. Individuals who had filled a prescription for anti-inflammatory drugs had an 85% reduced odds of having a diagnosis of ARMD (odds ratio 0.15, 95% confidence interval 0.12–0.18).

Conclusions. The results of this study suggest that veterans who had filled a prescription for anti-inflammatory medications had a reduced risk of ARMD. Further studies are needed to confirm this result.
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Key Words: age-related macular degeneration, medication, anti-inflammatory, prevention

Age-related macular degeneration (ARMD) is the leading cause of irreversible vision loss in United States and most western countries.[1] Anticipated increases in the elderly population in these countries are expected to result in large numbers of individuals who will become visually impaired over the next several decades.[2] Although strategies are emerging for treating and reducing end-stage disease, the changing demographics of the United States population has intensified the need for better understanding of possible interventions in the early stages of ARMD. The role of inflammation in the development of ARMD has received increasing attention in both epidemiological and basic histopathology studies. The work of Penfold et al., Johnson et al., Anderson et al.[1–3] and others has found a variety of immunomodulatory components associated with drusen. Local inflammation and complement activation seems to play a key role in the development of drusen as a result of damage to retinal pigment epithelial cells.[3] Similarly, epidemiological studies have shown a possible role for inflammation in the development of ARMD. Seddon et al.[4] have shown an association between C-reactive protein and ARMD. Klein et al.[5] found associations between the known chronic inflammatory conditions gout and emphysema with ARMD. Kalayoglu et al.[6] in a small study has found an association between *Chlamydia pneumoniae* antibodies and ARMD. Chlamydia has been proposed as a pro-inflammatory risk factor for cardiovascular disease.

METHODS

A nested case control study was conducted to evaluate the association between ARMD and anti-inflammatory medication use. The study cohort was male patients over the age of 50 who had at least one visit (inpatient or outpatient) to the Birmingham (Alabama) Veteran's Administration Medical Center (BVAMC) during the period January 1, 1997 to December 31, 2001. The BVAMC is a 134 bed acute care medical facility housing depart-

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ments of ophthalmology, optometry, and a regional blind rehabilitation center. Women were excluded due to low numbers within the veteran population. Veterans with ARMD diagnosis before 1997 (i.e., prevalent cases) were excluded. Electronic administrative data files containing demographic, clinical, medication, and prescription information were obtained from the BVAMC. The clinical data file contains information on each diagnosis and its date. Similarly, the medication file contains information on prescription and non-prescription medication, and date the prescriptions were filled within the BVAMC pharmacy. These administrative files contain information on all visits at the BVAMC including those before the study period 1997 to 2001. Through the use of this database it is possible to link clinical diagnostic, demographic and medication information without identification of individuals. In this way, diagnoses and medication history before 1997 could be reviewed to determine the presence or absence of ARMD and specific medication usage. Similarly linked files were reviewed between 1997 and 2001 to determine a date of first macular degeneration diagnosis.

Cases were individuals who presented with incident ARMD during the study period as identified by International Classification of Disease, Ninth Revision (ICD-9) codes 362.50, 362.51, and 362.52, respectively. All cases were assigned an index data based on the date of initial ARMD diagnosis (i.e., incident cases) during the study period. All controls were active patients at the BVAMC at the time the index case was diagnosed and were randomly selected from the BVAMC population and matched to cases by age (± 1 year). All controls were free of the diagnosis of ARMD based on ICD-9 at the time their matched case was diagnosed. At least seven controls were matched to each case. Each control was matched to a single case and considered to have the same index date as the corresponding subject. In some instances, more controls were matched based on the availability of a suitable control by the case index date and age.

Medications with anti-inflammatory properties include a variety of agents including steroids, non-steroidal anti-inflammatories, and salicylates among others. A complete formulary of all medications prescribed at the BVAMC during the study period was obtained and a list of anti-inflammatory medications was generated. Each medication on the formulary list was reviewed for anti-inflammatory properties based on active ingredient as listed in Drug Facts and Comparisons, and a comprehensive list of all medications with anti-inflammatory properties was generated.[7] Any oral, injectable, or inhaled medication with listed anti-inflammatory properties was included. Topical ophthalmic, dermatologic, and otic preparations were excluded from the anti-inflammatory category due to short-term usage and low potential for systemic absorption. Subjects were considered to have a history of anti-inflammatory medication use if they filled at least one prescription from the BVAMC pharmacy before the index date, including all prior BVAMC visits.

Conditional logistic regression was used to calculate odds ratios and 95% confidence intervals for the association between any anti-inflammatory medication use and ARMD. Analysis of individual drug usage was evaluated where sufficiently large numbers were available. Multivariate analyses were conducted adjusting for arthritis, diabetes, lipid metabolism, hypertension, cardiovascular disease, cerebrovascular disease, and arterial disease; each was defined by ICD-9 codes associated with that diagnostic category.

TABLE 1.
Demographic data

	Case (n = 614)	Controls (n = 4526)	p
Age, mean (SD)	72.9 (6.8)	73.2 (6.7)	0.80
Race, % (n)			
White	83.7 (514)	51.1 (2312)	
Black	5.5 (34)	16.6 (752)	
Other	0 (0)	0.3 (12)	
Unknown	10.8 (66)	32.0 (1450)	
Medical characteristics, n (%)			
Arthritis	37.5 (230)	28.1 (1273)	<0.0001
Diabetes	23.6 (145)	22.5 (1016)	0.53
Lipid metabolism	10.4 (64)	20.8 (940)	<0.0001
Hypertension	57.2 (351)	57.9 (2622)	0.72
Cardiovascular disease	29.5 (181)	31.8 (1437)	0.26
Cerebrovascular disease	4.1 (25)	10.4 (472)	<0.0001
Arterial disease	6.0 (37)	10.5 (476)	0.0005

RESULTS

By design cases and controls were similar in age, but mean age of controls was slightly older. More cases of arthritis were found ($p < 0.01$). Controls were found to have more disorders of lipid metabolism ($p < 0.01$), cerebrovascular disease ($p < 0.01$), and arterial disease ($p < 0.01$) (Table 1).

Among veterans with a diagnosis of ARMD 24% have filled a prescription for any of the anti-inflammatory drugs compared with 60% in the control population. Individuals who had a prescription filled for one of the drugs in the anti-inflammatory category had an 85% (odds ratio 0.15, 95% confidence interval 0.12–0.18) reduced odds of ARMD diagnosis after controlling for potential confounding. A total of 18 individual medications with anti-inflammatory properties meeting the study criteria had prescriptions filled at the BVAMC. All the individual anti-inflammatory drugs that had prescriptions filled showed point estimates in the direction of reduced risk of ARMD with the exception rofecoxib. A small number of prescriptions had been filled for rofecoxib ($n = 13$) and the increased risk of ARMD was not statistically significant ($p = 0.65$). Magnesium sulfate, diflunisal, and hydrocortisone had no prescriptions filled among the cases, although total numbers filled were small among controls for diflunisal and hydrocortisone. Non-significant associations for reduced ARMD risk were found for methylprednisolone ($p = 0.06$), fluticasone ($p = 0.13$), and nabumetone ($p = 0.06$). Diclofenac, dexamethosone, and celecoxib were used in such small numbers as preventive meaningful individual analysis, although all had non-statistically significant associations with ARMD (Table 2). Due to limitations of the database drug class effects, such as those of the cyclo-oxygenase 2 inhibitors could not be evaluated.

DISCUSSION

Our research suggests that anti-inflammatory drug use may reduce the risk of ARMD development. The potential of anti-

TABLE 2.
Anti-inflammatory drug use and macular degeneration

Drug	Cases (n = 614), %	Controls (n = 4526), %	OR	95% CI	p
Any	150 (24)	3051 (67)	0.15	0.12–0.18	<0.0001
Aspirin	104 (17)	2115 (47)	0.23	0.18–0.29	<0.001
Fluticasone	2 (0.33)	43 (0.95)	0.34	0.08–1.4	0.13
Indomethocin	11 (2)	300 (7)	0.26	0.14–0.49	<0.0001
Ibuprofen	64 (10)	1339 (30)	0.31	0.21–0.47	<0.0001
Methylprednisolone	3 (0.49)	67 (1.5)	0.32	0.1–1.03	0.06
Nabumetone	3 (0.49)	67 (1.5)	0.32	0.1–1.03	0.06
Naproxen	55 (9)	886 (20)	0.31	0.21–0.47	<0.0001
Prednisone	25 (4)	549 (12)	0.31	0.21–0.47	<0.0001
Salsalate	12 (2)	193 (4)	0.48	0.26–0.86	0.01
Oxaprozin	16 (3)	264 (6)	0.45	0.27–0.75	0.002
Piroxicam	10 (2)	239 (5)	0.32	0.17–0.60	0.0004

Controlled for arthritis, arterial disease, cardiovascular disease, diabetes, lipid metabolism, hypertension.

inflammatory drugs in reducing the risk of ARMD is biologically plausible. Histopathological evidence supports an inflammatory role in ARMD.[1–3] Data from the Rotterdam Eye Study population suggests that individuals who are homozygous for the gene coding for complement factor H Y4202H have a 48% risk of ARMD by age 95.[8] The data further suggested this gene may be a casual factor in more than 50% of cases of ARMD. The effect of this gene was shown to be modified by the known pro-inflammatory factors elevated erythrocyte sedimentation rate, elevated C-reactive protein levels and history of smoking.

A number of previous studies have looked at drug associations with ARMD. Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors), in particular, have been intensely studied for their possible protective effect in ARMD. In addition to their known cholesterol lowering effects, statins are known to have a number of pleiotrophic effects.[9] Most of these pleiotrophic effects are thought to act through the suppression of inflammation.[10] The results of these statin studies have been mixed. Evidence from the Beaver Dam, Blue Mountains, Cardiovascular Health Study, and Rotterdam studies have suggested no effect of statins on the 5 year incidence of ARMD.[11–14] Positive studies have suggested between a 13 and 70% risk reduction associated with statin use.[15,16]

Five previous epidemiological studies have looked at the association of drugs with anti-inflammatory effects and ARMD. Christen et al.[17] found no association of low dose aspirin use with reduced risk of ARMD in participants in the Physicians Health Initiative. Although the associations between aspirin use and ARMD showed risk reduction none were statistically significant. The number of ARMD cases was low due to the early termination of the trial. Christen and the authors pointed out that a possible protective effect could not be ruled out. Wilson et al.[15] in a small case control study within the Veterans health system also found a 37% risk reduction for ARMD among aspirin users. Klein et al.[10] found no association of anti-inflammatory medication use with ARMD in subjects in the Beaver Dam Eye Study. Wang et al.[18] found no association between steroid or anti-inflammatory medication use and both the presence and 5 year incidence of ARMD in the Blue Mountain Study. In the most recently published epidemiological study, in the area a strong protective effect of anti-inflammatory drugs was seen in the age-related eye disease study population.[19] A 78% risk reduction was found for advanced central geographic atrophy among anti-inflammatory drug users. The study did not define which drugs were counted in the anti-inflammatory category.

The results from this study follow those of Wilson and Clemons et al., and do support a strong protective effect for at least some of the anti-inflammatory drugs. Due to the nature of the study population and the limitations of our dataset the results should be viewed with some caution. Any study conducted within the Veteran's Administration health system has inherent selection bias. Case identification was based on clinical ICD-9 coding by multiple clinicians. Variability between clinicians may have allowed for some misclassification between early cases of dry ARMD and controls. Due to the lack of standard clinical definition for early ARMD some at this stage could have been coded in either case or control groups. In particular, drusen were not included as ARMD cases by our definition. It is also possible that some misclassification could have occurred with subjects who had diagnosis by doctors outside the veteran's health system. Since any misclassification that occurred was in both directions, it is unlikely that any systematic errors resulted. Most studies of drug use and disease associations rely on self report of medication. This study is unique in which medication use was based on filled prescriptions. The filling of a prescription does not assure use but may be more accurate than self report. Potentially, some misclassification may also have occurred as a result of prescriptions filled outside the BVAMC pharmacy system. Due to the limitations of the data set control for other potential factors, including race, smoking, and anti-oxidant levels, could not be controlled and may have resulted in some residual confounding. It is also possible that the underlying disease necessitating the use of anti-inflammatory medication may itself in some way impact the risk of ARMD. If disease states necessitating the use of anti-inflammatory agents increase the risk of ARMD, the potential benefits of anti-inflammatory agents may have been underestimated. The principle cause of anti-inflammatory use, arthritis was controlled for in the analysis. Case control studies do have inherent problems with temporal associations of the risk factor and outcome. All cases identified were incident and use of anti-

inflammatory drugs had been present before the diagnosis of ARMD. The current data allowed the determination of which drugs were used but the duration of the use was unavailable and did not allow for evaluation of dose response effects.

Our results provide additional support for the role of at least some anti-inflammatory agents in reducing the risk of ARMD. If confirmed they would offer another avenue of potential reduction in the disease burden along with vitamin and anti-oxidant supplements. More carefully controlled clinical studies in the area are needed to support or discount the need for a clinical trial.

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