The Relationship Between Nonsteroidal Anti-inflammatory Drug Use and Age-related Macular Degeneration

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• PURPOSE: To describe the relationship between the incidence of age-related macular degeneration (AMD) and nonsteroidal anti-inflammatory drug (NSAIDs) use.
• DESIGN: Prospective cohort study.
• METHODS: This study consisted of participants in the California Men's Health Study. Those who completed surveys in 2002-2003 and 2006 were included. Men who self-reported use of aspirin, ibuprofen, naproxen, valdecoxib, celecoxib, and/or rofecoxib at least 3 days per week were considered NSAID users. Patients were categorized as non-users, former users, new users, or longer-term users based on survey responses. NSAID use was also categorized by type: any NSAIDs, aspirin, and/or non-aspirin NSAIDs. Age, race/ethnicity, smoking status, education, income, alcohol use, and Charlson comorbidity index score were included in the multivariate analysis as risk factors for AMD.
• RESULTS: A total of 51 371 men were included. Average follow-up time was 7.4 years. There were 292 (0.6%) and 1536 (3%) cases of exudative and nonexudative AMD, respectively. Longer-term use of any NSAID was associated with lower risk of exudative AMD (hazard ratio [HR] 0.69, 95% confidence interval [CI] 0.50-0.96, $P = .029$). New users of any NSAIDs (HR = 0.79, 95% CI 0.68-0.93, $P = .0039$) and aspirin (HR = 0.82, 95% CI 0.70-0.97, $P = .018$) had a lower risk of nonexudative AMD, although this trend did not persist in longer-term users. The relationship between exudative or nonexudative AMD and the remaining categories of NSAID use were not significant.
• CONCLUSION: The overall impact of NSAIDs on AMD incidence is small; however, the lower risk of exudative AMD in longer-term NSAID users may point to a protective effect and deserves further study as a possible mechanism to modulate disease risk. (Am J Ophthalmol 2018;188:111–122. © 2018 Elsevier Inc. All rights reserved.)

AGE-RELATED MACULAR DEGENERATION (AMD) IS a leading cause of blindness in the elderly.[1] Risk factors for macular degeneration include age, smoking, diet, and genetics. Several single nucleotide polymorphisms related to inflammation have been identified as possible risk factors.[2] Inflammation and inflammatory cells[3] have been implicated in the pathogenesis of AMD, which intuitively would suggest that nonsteroidal anti-inflammatory drugs (NSAIDs) may be a modulator of disease activity.[4]

There is considerable controversy in the literature on the association between NSAIDs and AMD, with most studies finding either a modest increase in risk or no relationship.[5–7] The overwhelming majority of investigations have focused on aspirin use while neglecting the possible role of other NSAIDs in AMD. To address the limitations in the literature, we undertook a study within a prospective cohort nested in an integrated healthcare delivery system.

METHODS

THIS IS A PROSPECTIVE COHORT STUDY OF PARTICIPANTS IN the California Men's Health Study (CMHS), which was conducted in Kaiser Permanente Southern and Northern California.[8] Kaiser Permanente is an integrated group-practice prepaid health plan. Details of the CMHS design and characteristics of the men included have been previously described.[8] This cohort consists of men between 45 and 69 years old at the time they completed a baseline self-administered questionnaire between January 2002 and December 2003 and who subsequently responded to a follow-up survey in 2006. Eligible health plan members were initially mailed a recruitment letter and a screener questionnaire. The 134 060 participants who completed the screener questionnaire were then mailed the full baseline questionnaire, which was completed by 84 140 participants. These questionnaires assessed information

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on sociodemographic factors, personal and family cancer history, healthcare utilization, health conditions, select medication use (including over-the-counter drugs), tobacco use, and alcohol use, as well as diet and physical activity. Participants, approximately 40% of whom self-reported being nonwhite, closely reflected the sociodemographic diversity of men residing in California.[8] A follow-up survey was sent in 2006 that was completed by 55 952 of the men who completed the baseline 2002-2003 survey. The study was approved by the institutional review boards of Kaiser Permanente Southern and Northern California and complied with the principles of the Declaration of Helsinki.

Data on race/ethnicity, body mass index (BMI), smoking status, and history of diabetes, hyperlipidemia, peripheral vascular disease, and heart attack were taken from survey responses. Age was also taken from survey responses unless it was not filled out, in which case it was retrieved from the electronic medical record. Charlson comorbidity index score[9] and diagnosis of AMD (exudative and nonexudative) were taken from the electronic medical record. Incident AMD was identified in the health plans' electronic medical records as a new diagnosis made by an ophthalmologist following completion of the 2006 survey with International Classification of Disease (ICD)-9 codes 362.52 (exudative AMD) and 362.51 (nonexudative AMD). Patients were followed until the earliest occurrence of patient death, patient disenrollment from the Kaiser Permanente health plan, or July 31, 2015. Patients with a diagnosis of AMD that occurred prior to the 2006 survey were excluded. Patients were considered NSAID users if they indicated use of aspirin, ibuprofen, naproxen, valdecoxib, celecoxib, and/or rofecoxib at least 3 times per week.

NSAID use was characterized as follows: (1) longer-term users were those who indicated NSAID use on both the 2002 and 2006 survey; (2) new (or shorter-term) users were those who indicated NSAID use on the 2006 but not the 2002 survey; (3) former users were those who indicated NSAID use on the 2002 but not 2006 survey; and (4) non-users were those who did not indicate NSAID use on any survey.

Age, race/ethnicity, smoking status, Charlson comorbidity index score, education level, income, and alcohol use were included in the multivariate analysis as risk factors for AMD and potential confounders for analysis of NSAID effect.

Patient characteristics were described using standard descriptive statistics. Associations were assessed using the χ^2 test for categorical factors and the Wilcoxon rank sum test for continuous variables. The Cox proportional hazards model was used to assess the overall association of NSAID use and AMD adjusted for confounders. Separate models were created to analyze associations based on type of NSAID use—patients were divided into groups of any NSAID use, aspirin use, and/or non-aspirin NSAID use. Analysis were conducted using SAS Enterprise Guide version 5.1 (SAS Institute Inc, Cary, North Carolina, USA).

RESULTS

OF THE 84 170 MEN WHO COMPLETED THE BASELINE 2002-2003 survey, 55 952 completed the 2006 follow-up survey. Nine hundred and forty of these men were excluded owing to already having a diagnosis of AMD at the time of the 2006 survey. The prevalence of nonexudative AMD was 1.8% among any NSAID users, 1.8% among aspirin (ASA) users, 1.7% among non-ASA NSAIDs users, and 1.5% among non-users at the time of the 2002 survey. The prevalence of exudative AMD was 0.21% among any NSAID users, 0.24% among ASA users, 0.13% among non-ASA NSAID users, and 0.19% among non-users at the time of the 2002 survey. Table 1 provides a summary of patients who were diagnosed with AMD between the 2002 and 2006 surveys. Three thousand six hundred and forty-one men were excluded from the study because they were no longer health plan members at the time of the 2006 survey. A total of 51 371 men were included in our cohort. The average follow-up time was 7.4 years. Baseline characteristics are provided in Table 2.

TABLE 1. Patients Diagnosed With Age-related Macular Degeneration Between 2002 and 2006 Surveys

	Non-users	Former Users	New (Shorter-term) Users	Longer-term Users	χ^2
Exudative AMD					
Any NSAID use	35 (0.13%)	10 (0.13%)	8 (0.09%)	17 (0.15%)	.6655
ASA	38 (0.11%)	10 (0.17%)	7 (0.09%)	15 (0.19%)	.1847
Non-ASA NSAID	63 (0.14%)	2 (0.05%)	3 (0.07%)	2 (0.07%)	.1665
Nonexudative AMD between 2002 and 2006					
Any NSAID use	235 (0.85%)	64 (0.84%)	99 (1.07%)	114 (0.99%)	.1734
ASA	293 (0.85%)	53 (0.91%)	83 (1.08%)	83 (1.04%)	.1466
Non-ASA NSAID	401 (0.90%)	37 (0.83%)	50 (1.11%)	24 (0.90%)	.5154

AMD = age-related macular degeneration; ASA = aspirin; NSAID = nonsteroidal anti-inflammatory drug.