As more data point to protection against melanoma and NMSC, clinical implications are still limited.

BY JONATHAN WOLFE, MD

A new study adds to the growing body of evidence that the use of non-steroidal anti-inflammatory drugs (NSAIDs) may be associated with a modest reduction in an individual’s risk for developing malignant melanoma (MM) and non-melanoma skin cancer (NMSC). These findings continue to suggest that the issue of NSAIDs and skin cancer risk warrants continued study and may eventually reveal a novel therapeutic approach to skin cancer prevention.

THE POSITIVE EVIDENCE THUS FAR

One promising study found NSAID use to be associated with a modestly reduced risk of squamous cell carcinoma (SCC). Specifically, NSAID use seemed to reduce the risk of SCC tumors with p53 or PTCH mutations in the population-based, case-control study involving 1,484 participants. Aspirin use provided the greatest reduction in risk; patients who had been taking the drug for six years or less experienced the greatest benefit. While researchers identified a slightly reduced risk of basal cell carcinoma (BCC) associated with the use of aspirin or paracetamol (acetaminophen; an analgesic though not a true NSAID), there was no association between NSAID use and BCC risk overall.

A double-blind, placebo-controlled, randomized trial involving 240 subjects ages 37-87 diagnosed with 10-40 AKs investigated the potential utility of the cyclooxygenase-2 (COX-2) inhibitor celecoxib as a chemopreventive agent for actinic keratoses (AK) and NMSC. Patients were randomly assigned to receive 200mg of celecoxib or placebo orally twice daily for nine months. At nine months, the incidence of AKs was similar between the two groups. At 11 months, however, patients in the treatment arm had fewer NMSCs than did controls, even after adjusting for age, sex, Fitzpatrick skin type, history of AK at randomization, NMSC history, and patient time on study. Treated patients also had lower rates of both SCC and BCC compared to controls. The use of COX-2 inhibitors was not associated with any increase in the rate of serious and cardiovascular adverse events compared to controls.

Data link longer-term (more than five years) aspirin use with a significant reduction in melanoma risk compared to infrequent NSAID use or non-use. The protective benefit was observed after adjustment for confounders in a cohort of 400 melanoma patients and 600 age- and gender-matched, community-based controls. The same study investigated any effect of statin use on melanoma risk and found none.

In 2009, Joosse, et al. reported that continuous use of low-dose aspirin was associated with a reduced incidence of cutaneous melanoma in women but not in men. Their conclusions were based on a case-control study of individuals in the Dutch PHARMO pharmacy database and a national pathology database. Cases of primary cutaneous melanoma diagnosed between 1991 and 2004 in individuals 18 or older with three years of pre-diagnosis PHARMO data were analyzed. Age-, sex-, and geographical region-matched controls were selected. A total of 1,318 cases of melanoma and 6,786 controls were analyzed. The only association between NSAID use and melanoma risk in these patients was a significant decrease—relative to controls and to aspirin non-users or non-continuous users—in melanoma risk for women who had continuously used low-dose aspirin. Similar trends were not seen in men.

The latest data show a reduction in risk of melanoma and NMSC associated with use of NSAIDs. The study authors identified all incident cases of SCC (n=1,974), BCC (n=13,316), and MM (n=3,242) from 1991 through 2009 in northern Denmark, which they matched to approximately 10 population controls (n=178,655) by age, gender, and county of residence. Through a prescription database, they ascertained subjects’ use of aspirin, other non-selective NSAIDs, or selective COX-2 inhibitors. Conditional logistic regression analyses adjusted for potential confounders were used to compute odds ratios as estimates of incidence rate ratios (IRRs).

Overall, use of NSAIDs (>2 prescriptions) compared with nonuse (<2 prescriptions) was associated with a decreased risk of SCC (IRR, 0.85; 95% confidence interval [CI], 0.76-0.94) and MM (IRR, 0.87; 95% CI, 0.80-0.95). The benefit was particularly associated with long-term use (seven years or more) and high-intensity use. Although NSAID use was not associated with a reduced risk of BCC overall (IRR, 0.97; 95% CI, 0.93-1.01), long-
term and high-intensity use were associated with reduced risk of BCC at sites other than the head and neck (IRR, 0.85; 95% CI, 0.76-0.95; IRR, 0.79; 95% CI, 0.69-0.91, respectively).

MORE THAN SKIN DEEP

The anti-cancer benefits of NSAIDs seem not be limited to cutaneous malignancies. In an earlier publication, researchers looking at the Vitamins and Lifestyle (VITAL) cohort of 63,809 men and women found no association between NSAID use and melanoma incidence after adjusting for melanoma risk factors and indications for NSAID use.\(^6\) However, data from the same cohort suggest that the use of NSAIDs may reduce the incidence of total cancer among men and colorectal cancer among both sexes. This time, researchers analyzed data for 64,847 residents of western Washington State, aged 50-76. NSAID use was categorized as non-use, low (<4 days/week for <4 years), and high (≥4 days/week and ≥4 years). Compared to non-use, high 10-year use of regular-strength NSAIDs was inversely associated with total cancer risk in men (HR, 0.88, 95% CI, 0.79-0.97) but not associated with risk in women. Use of regular-strength NSAIDs was strongly inversely associated with colorectal cancer risk in men and women.\(^7\)

Evidence of a potential protective effect of NSAIDs, as discussed previously in this column, is intriguing. Similar findings in the larger field of oncology are also promising. However, there is still much to learn. Why is the protective effect stronger in SCC—and perhaps even specific genotypes—than in BCC? Why, despite several studies suggesting protection from melanoma, have some studies\(^6\) found no benefit? Is it more effective to target COX-2, specifically, than to target COX-1 and -2, as aspirin does? It is also important to consider the study designs and study populations. These studies may select healthier patients who may avoid sun more than “normal controls” and thus the slightly lower risk of melanoma.

Without further evidence, we cannot use NSAIDs broadly for skin cancer prevention. However, NSAIDs may be an appropriate option for skin cancer prevention in certain high-risk patients with a history of cutaneous malignancies. Given the relatively low risk associated with NSAID use, daily aspirin intake with the goal of tertiary prevention of skin cancer may be reasonable—just as aspirin is used in patients at risk for cardiovascular disease.

Dr. Wolfe has no relevant disclosures.

Jonathan Wolfe, MD is Clinical Assistant Professor of Dermatology at the University of Pennsylvania in Philadelphia, PA where he is on the staff of the Pigmented Lesion Clinic. He is in private practice in Plymouth Meeting, PA.