Aspirin and Familial Adenomatous Polyposis: Coming Full Circle

Andrew T. Chan

Abstract

This perspective discusses the clinical trial reported by Burn and colleagues in this issue of the journal (beginning on page 655), which assessed aspirin and resistant starch for the prevention of colorectal adenomas in patients with familial adenomatous polyposis (FAP). The findings are examined in the context of previous clinical trials of aspirin in patients with sporadic adenomas and of sulindac or celecoxib in patients with FAP. This newly reported work raises important considerations of a role for aspirin in the clinical management of FAP patients and adds to considerations of a role for aspirin in the chemoprevention of colorectal cancer among broader populations. Cancer Prev Res; 4(5); 623–7. ©2011 AACR.

Introduction

Although familial adenomatous polyposis (FAP) accounts for less than 1% of colorectal cancers, this hereditary colorectal cancer syndrome has provided tremendous insight into the pathogenesis of sporadic colorectal cancer. The key distinguishing feature of classic FAP is the development of hundreds to thousands of adenomatous polyps throughout the colon, often beginning as early as the second decade of life. Colorectal adenocarcinomas inevitably develop in FAP patients, typically by age 40, or approximately 10 to 15 years after the initial appearance of polyposis. In the general U.S. population, sporadic colorectal adenomas arise in approximately 50% of men and 30% of women by age 50, and most diagnosed individuals have only a few polyps over their lifetimes (1). Although the vast majority of sporadic colorectal cancers arise from adenomas (2), it is estimated that the annual rate of adenocarcinoma development is as low as 2.5 per 1,000 adenoma-bearing individuals overall (3).

As an accelerated clinical manifestation of the adenoma to carcinoma sequence that characterizes the development of most colorectal cancers (2), FAP provides a window into the genetic and molecular pathogenesis of sporadic colorectal neoplasia. The germline mutation underlying FAP is transmitted in an autosomal dominant manner, with nearly 100% of affected individuals developing polyposis. In 1991, 3 groups identified germline mutations in the adenomatous polyposis coli (APC) gene on chromosome 5q21 as the genetic alteration underlying FAP (4–6). This discovery led to dramatic advances in our understanding of the molecular events underlying not only FAP but also the 80% of sporadic colorectal cancers typified by somatic mutations of both APC alleles. Disruption of the APC gene subsequently was identified as an early molecular event and key driver of somatic chromosomal abnormalities. On the basis of these shared molecular underpinnings, FAP has become an attractive model for testing agents, including aspirin and other, “aspirin-like” nonsteroidal anti-inflammatory drugs (NSAID) such as sulindac, indomethacin, and piroxicam, all of which inhibit prostaglandin synthesis (7), for their chemopreventive potential against sporadic colorectal cancer.

The importance of prostaglandin pathways in colorectal carcinogenesis and the antitumor effects of NSAIDs initially emerged through in vitro and animal studies (8), leading to the first report of sulindac inducing regression of colon polyps in 4 FAP patients from a single family in 1983 (9). This observation, plus similar results of several other uncontrolled clinical studies, led to randomized, placebo-controlled trials of sulindac in FAP patients that have shown significant decreases in the number and size of polyps (10–12). Based in part on these findings, sulindac has been successfully applied in combination with the polyamine synthesis inhibitor difluoromethylornithine (DFMO) for prevention in the setting of sporadic adenomas. In a landmark randomized, double-blind, placebo-controlled clinical trial in 375 patients with prior adenomas, 3 years of daily treatment with sulindac (150 mg) and DFMO (500 mg) reduced the risk of recurrent adenomas by an impressive 70% compared with placebo (13).

The FAP model has also played an instrumental role in elucidating COX-2 as a key molecular target of aspirin and NSAIDs. Aspirin and other NSAIDs have been shown to directly inhibit adenomas in an animal model of FAP, the multiple intestinal neoplasia mouse derived from mutations in the APC gene (14–16). Knockout of the COX-2 gene or pharmacologic COX-2 inhibition in APCMin mice dramatically reduced the number of polyps (17). Taken together with findings that COX-2, but not
COX-1, is overexpressed in human colorectal adenomas and cancers (18). These findings suggest the likelihood that the anticancer effect of aspirin and other NSAIDs is, at least in part, mediated through inhibition of COX-2 pathways (19). Nonetheless, other data suggest that non-COX mechanisms unique to either aspirin or other NSAIDs may also be important in mediating their antitumor effect (20–23).

With the promise of a molecular-targeted approach and an improved gastrointestinal safety profile, agents with COX-2 selectivity were tested for chemopreventive efficacy in FAP. As reported in 2000, a randomized placebo-controlled trial of the COX-2-selective inhibitor celecoxib (400 mg twice daily for 6 months) produced a 28% reduction in the mean number of colorectal polyps and a 31% reduction in polyp size in 77 FAP patients (24). This study led to Food and Drug Administration (FDA)-accelerated approval of a labeled indication for celecoxib as an adjunctive treatment for FAP patients and provided convincing proof of principle for selective COX-2 targeting to inhibit neoplasia. These results were later extended to the prevention of sporadic adenomas. In 3 randomized, placebo-controlled trials completed in 2005–2006, celecoxib and another COX-2-selective inhibitor, rofecoxib, significantly reduced adenoma recurrence among patients with a prior history of adenoma (25–27). Unfortunately, the Adenoma Prevention with Celecoxib trial found a dose-dependent, 3-fold higher risk of cardiovascular events in patients taking celecoxib (28, 29) and a comparable association occurred in the similarly designed Adenomatous Polyp Prevention on Vioxx (rofecoxib; APPROVe) trial (30, 31). These adverse event findings led to the withdrawal of rofecoxib from the market and an FDA-mandated black box warning for celecoxib. Recent data have shown that nonselective NSAIDs such as sulindac and naproxen may also be implicated in increased cardiovascular thrombotic risk (32–34). On the basis of these findings of concern, it is unlikely that prolonged use of COX-2–selective inhibitors and certain other NSAIDs for colorectal cancer chemoprevention is a viable strategy for a generally healthy population with access to other highly effective screening and prevention modalities (35). However, efforts to characterize patients who may be at a lower risk of NSAID-related cardiovascular toxicity or at a particularly high risk of sporadic colorectal cancer (e.g., patients with larger or histologically advanced adenomas) may eventually lead to chemopreventive NSAID programs tailored to specific patient populations with favorable risk-benefit profiles (29, 34, 36).

Concerns about NSAID-associated cardiovascular toxicity have also refocused attention on the chemopreventive properties of aspirin, the oldest of the “modern” anti-inflammatory drugs. Aspirin not only has a favorable cardiovascular profile but is already widely used for the prevention of cardiovascular events (37). Therefore, the results of the Colorectal Adenoma/Carcinoma Prevention Programme 1 (CAPP1) trial reported by Burn and colleagues in this issue of the journal are particularly timely (38). These investigators conducted a randomized, placebo-controlled trial of daily aspirin (600 mg) and/or resistant starch (30 g) in a 2-by-2 factorial design in 206 FAP patients. Among 133 patients who were evaluable because they underwent at least 1 follow-up lower endoscopy, there was no significant reduction in polyp count (the primary endpoint) or size of the largest polyp (secondary endpoint) with either intervention. Although these overall results may seem disappointing, closer scrutiny of the data reveals several important findings that lend additional support for an anticancer benefit of aspirin. First, there was a nonsignificant reduction in polyp number associated with aspirin treatment (relative risk = 0.77; 95% CI, 0.54–1.10) compared with nonaspirin. Second, there was a trend toward a reduction in size of the largest polyp in patients of the aspirin group treated for 1 or more years (compared with nonaspirin; adjusted P for difference = 0.09). Last, there was a significant reduction in polyp size among patients treated with aspirin for more than 1 year (compared with nonaspirin; adjusted P for difference = 0.02), a group of patients that might reasonably be expected to have been more compliant with daily aspirin than were patients who did not elect to continue in the study beyond the first year. These positive trends are even more remarkable because they showed up despite several limitations of the study. These limitations included a lack of standardization of the extent of endoscopic examination (sigmoidoscopy vs. full colonoscopy); surveillance done by multiple endoscopists at 12 different treatment centers; and the prolonged, 9-year time period of the study. Each of these issues would be expected to introduce significant variability, especially in outcome ascertainment, causing a substantial underestimation of a potential effect of the aspirin intervention. In contrast, prior clinical trials that did show strong benefits for sulindac and celecoxib among FAP patients ascertained endpoints using a standardized protocol by a few specially trained endoscopists within a limited number of centers over only short-term (6–9 months) follow-up (11, 24).

The largest reported clinical trial in patients with FAP, this study was a heroic effort not least because of the extraordinary difficulty in recruiting 133 evaluable patients with a genetic condition that affects no more than 1 in 10,000 to 30,000 individuals. Indeed, this difficulty led the manufacturer of celecoxib in February 2011 to voluntarily withdraw the FAP indication from its FDA-approved labeling because of a delay in completing the follow-up trial required under its accelerated initial approval.

It is notable that the rigorous clinical trials of sulindac and celecoxib showing efficacy in the high-risk population of FAP patients served as the initial proofs of principle clinical trials that motivated studies of these agents in lower-risk populations of sporadic adenoma patients. In contrast, there have been no clinical trials of aspirin in FAP patients prior to that of Burn and colleagues, and 4 completed randomized, placebo-controlled trials have already shown that aspirin reduces the risk of sporadic adenoma recurrence (39–42). A recent meta-analysis of these trials found that aspirin users had a pooled risk ratio of 0.83 (95% CI,
files. A pooled analysis of 6 randomized controlled trials of many FAP patients considering chemoprophylaxis are the potential for cardiovascular toxicity associated with reasonable option, which may hold some appeal in light of Burn and colleagues suggest that aspirin may be another agents considered for adjunctive therapy of FAP. The data perhaps even in the duodenum.

Pharmacologic intervention in reducing the number and treatment, there remains a potential adjunctive role for mias in the gastrointestinal tract is the cornerstone of FAP fore, although intensive screening and resection of adeno-

mas in the gastrointestinal tract would help define the precise role of long-term chemoprevention in the high-risk population of FAP patients who have had a prophylactic colectomy.

The study by Burn and colleagues has greater implications by providing yet another key piece of evidence supporting a potential role for aspirin chemoprevention in the broader population. This evidence complements not only the consistent results of the 4 clinical trials of aspirin in sporadic adenomas but also a substantial body of evidence showing that aspirin lowers the risk of colorectal cancer. Although the Physicians' Health and Women's Health studies did not find a benefit of aspirin against colorectal cancer (48, 49), these findings could reflect the use of low doses of aspirin every other day, rather than daily or insufficient duration of treatment or follow-up. In support of this explanation, large, prospective studies (50, 51), as well as secondary analyses of data from randomized trials of aspirin conducted for cardiovascular disease prophylaxis, have found that long-term use of aspirin is associated with a lower risk of incident colorectal cancer or death from colorectal cancer (52, 53). Recent data also support a role for aspirin in improving survival among patients with colorectal cancer (54). Last, further supportive data come from the CAPP2 Study of aspirin (600 mg/d) in patients with Lynch syndrome, a distinct autosomal dominantly inherited condition in which germline mutations in mismatch repair genes confer a high lifetime risk of cancers of the colorectum as well as other organs, including the uterus, small intestine, and ovaries. Although aspirin did not reduce the risk of colorectal adenoma or carcinoma over a mean treatment duration of 29 months, there was a nearly 40% aspirin-associated reduction in the risk of Lynch-related cancers in the longer term (more than 120 months of follow-up; refs. 55, 56). These clinical results are supported by recent aspirin data in a mouse model of Lynch syndrome (57). Comparable data for long-term use of sulindac or celecoxib in relation to the risk of sporadic or Lynch-related colorectal cancer are not available.

Despite this clear evidence of preventive benefit, current recommendations do not support the routine use of aspirin for prevention of colorectal cancer primarily because of concerns about gastrointestinal toxicity (37). These recommendations were developed, however, prior to recent data from long-term follow-up of 8 completed randomized trials of daily aspirin (originally conducted for vascular disease prevention) which
showed a compelling reduction in death because of all cancers, across several organ systems (58). Taken together with the known vascular benefits of aspirin, these results may tip the scale in favor of aspirin for many individuals as the agent of choice for chemoprevention of many cancers and vascular disease and their mortality. Therefore, recommendations about aspirin for prevention can no longer consider its effect on specific cancers in isolation. Nonetheless, substantial uncertainty remains about the optimal dose, duration and frequency of use, and age of initiation that can maximize the benefits of aspirin for both cancer and vascular indications while minimizing the risks (59). Until such questions are fully addressed, the decision on whether to use aspirin for chronic disease prevention remains highly individualized and based on the best available evidence at hand. In closing the circle of aspirin study in clinical settings from moderate to the highest risk of colorectal cancer, Burn and colleagues have contributed an important new piece of this evidence.

Disclosure of Potential Conflicts of Interest

The author has served as a consultant to Bayer Healthcare and is a Damon Runyon Clinical Investigator.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received February 15, 2011; revised March 20, 2011; accepted March 23, 2011; published online May 4, 2011.

References

Aspirin and Familial Adenomatous Polyposis: Coming Full Circle

Andrew T. Chan


Updated version
Access the most recent version of this article at:
http://cancerpreventionresearch.aacrjournals.org/content/4/5/623

Supplementary Material
Access the most recent supplemental material at:
http://cancerpreventionresearch.aacrjournals.org/content/suppl/2011/04/27/4.5.623.DC1

Cited articles
This article cites 59 articles, 18 of which you can access for free at:
http://cancerpreventionresearch.aacrjournals.org/content/4/5/623.full#ref-list-1

Citing articles
This article has been cited by 1 HighWire-hosted articles. Access the articles at:
http://cancerpreventionresearch.aacrjournals.org/content/4/5/623.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.