Editorial

The Adenoma Prevention with Celecoxib and Prevention of Colorectal Sporadic Adenomatous Polyps Trials: Stepping Stones to Progress

Ernest Hawk and Jaye L. Viner

Medical science and clinical practice progress through iterative cycles of discovery and translation. Through this process, cumulative insights into carcinogenesis at the nano/molecular level have radically transformed our views of health and illness and ignited demand for improved disease prediction, prevention, and personalization (1). Interactions within and across scientific disciplines will drive progress along the translational continuum from discovery to the successful development of new/reprogrammed clinical tools, or to ''productive failures'' (e.g., the generation of reliable, accurate data that do not confirm the initial hypothesis), most likely in a nonlinear manner. The presence versus absence of well-maintained linkages and clean hand-offs between disciplines and research cycles will govern the rate at which we progress toward achieving these goals.

The Adenoma Prevention with Celecoxib and Prevention of Colorectal Sporadic Adenomatous Polyps Trials

The development of celecoxib (a cyclooxygenase-2 inhibitor or COXIB) for colorectal adenomas is a recent case in point. Together, the Adenoma Prevention with Celecoxib (APC) and the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trials randomized more than 3,500 patients with prior adenomas to celecoxib (at one of three doses: 200 mg b.i.d, 400 mg q.d, or 400 mg b.i.d.) versus placebo for up to 3 years (2, 3). The trials were conceived, administered, and supported by collaborators from academia, National Cancer Institute, and industry and involved more than 200 clinical sites worldwide, creating a virtual network of clinical investigators, support staff, and monitors. Although the trials were independent, at specific junctures, the research teams worked together to assure that their data would meet rigorous scientific and regulatory standards. Both trials showed a statistically significant 33% to 45% reduction in recurrent colorectal adenomas, with greater effectiveness against advanced adenomas and in patient subsets (those with a personal history of large and/or multiple adenomas or a family history of colorectal cancer) presumed to be at higher risk for colorectal cancer. In addition, the trials inadvertently identified the potential for serious cardiovascular risks with celecoxib use (4, 5).

Despite resounding and mutually confirmed efficacy, intense focus on cardiovascular risks identified in these trials has prevented us from fully probing two key questions, the answers to which may mitigate uncertainty among chemoprevention investigators and suggest a way forward. First, what did these massive efforts (and investments) achieve? Second, where do we go from here?

What Was Achieved?

The immediate answer is obvious. Celecoxib was definitively shown to reduce adenoma recurrence in a dose-dependent manner and drew attention to an increased risk of cardiovascular events compared with placebo in patients with prior adenomas. Importantly, celecoxib was more effective against more advanced lesions and in patients at greatest risk for colorectal cancer. Demonstration of these effects is precisely what one would hope from a highly effective chemopreventive agent. In addition, the trials showed beneficial effects across a spectrum of pathologic features (i.e., adenoma size, number, and burden), providing a measure of internal validation for inferences of efficacy. That said, we must interpret these data with caution. Although the trials were inadequately powered to do so, neither showed efficacy against a longer-term goal of interest, reduction of colorectal cancer.

With regard to cardiovascular safety concerns, the APC trial showed an apparent adverse dose-response effect, with greater toxicity observed in patients receiving the higher dose. The PreSAP trial did not report a statistically significant difference in serious adverse cardiovascular events; however, it was not powered to do so. This result leaves open the important question as to whether the PreSAP trial's alternative dosing schedule (i.e., 400 mg daily), which was effective against colorectal adenomas, might convey significant cardiovascular risks. The APC and PreSAP trials, taken together with data from the Adenomatous Polyp Prevention on Vioxx trial (6) and various observational studies (7, 8), suggest that cardiovascular risks seen with celecoxib may also extend to other nonsteroidal anti-inflammatory drugs and COXIBs (e.g., etoricoxib and diclofenac). The clinical effect of these data on the public's health is difficult to estimate with precision. NSAIDs had been used for decades by millions of individuals worldwide to treat arthritis and pain before the emergence of these safety concerns. Although many NSAIDs/COXIBs are still appropriately used to treat these and other conditions, their risk/benefit profiles are now better defined. Indeed, cardiovascular risk characterization of NSAIDs/COXIBs may prove one of the more enduring contributions of this research cycle.

Furthermore, these phase III trial results provide a measure of validation for the models, strategies, and studies that preceded them. The identification of cyclooxygenase as a promising target and NSAIDs/COXIBs as a promising class of compounds was derived from several converging lines of evidence-mechanistic, preclinical, and observational (9). For example, celecoxib was shown to inhibit intestinal carcinogenesis in mice with adenomatous polyposis coli mutations (10) and in rats with carcinogen-induced neoplasia (11), suggesting the usefulness of both animal models in vetting promising

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Requests for reprints: Ernest Hawk, Division of Cancer Prevention, National Cancer Institute, EPN Suite 2141, 6130 Executive Boulevard, MSC 7317, Bethesda, MD 20892-7317. Phone: 301-594-2684; Fax: 301-435-6344. E-mail: eh51p@nih.gov

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chemopreventive agents despite differences in the site of disease (small intestine versus colon, respectively) and certain reservations on the part of researchers.

Finally, the APC and PreSAP trials generated data that may inform the design of other colorectal cancer prevention trials, particularly with respect to participant selection and the duration of exposure to test agents. First, the APC and PreSAP participants were at extraordinarily high risk for recurrent colorectal adenomas, which were found in approximately 50% to 60% of randomized individuals, exceeding recurrence rates reported from earlier trials of similar design (12-17). The enrollment of higher risk participants might reduce the number of patients needed for future trials as well as trial costs. Second and perhaps more importantly, the trials included *a priori* efficacy assessments at 12 and 36 months. That is, from trial inception, APC and PreSAP investigators postulated that the effects of a powerful agent with regressive (as well as suppressive) effects against colorectal neoplasia, as shown with NSAIDs in Apc min mice and suggested by a phase II trial in patients with familial adenomatous polyposis (18), might be measured sooner than the standard colonoscopic surveillance interval of 3 to 5 years. Indeed, both trials clearly showed efficacy of celecoxib by 12 months, which was later confirmed at 36 months, suggesting the efficiencies that the next generation of trials might achieve through early assessments. Early demonstration of clinical efficacy, if confirmed in subsequent trials testing a wider range of agents, would justify shorter chemoprevention trials, thereby accelerating translational progress and conserving critical resources.

Where Do We Go from Here?

Progress in translating science into practical tools that reduce the burden of cancer requires a continuous dialogue and exchange of ideas between scientists from many different backgrounds and perspectives. The APC and PreSAP trials have yielded an array of successes and productive failures. At this juncture, we can reasonably consider some of the translational questions that could, and should, be addressed by the next iteration of bench, population, and clinical research. The next cycle of inquiries will hopefully elucidate past results and suggest new hypotheses worthy of testing.

For bench research, key questions relate to mechanism(s) underlying the cardiovascular toxicities. While the imbalance between prostacyclin and thromboxanes was the initial focus of interest, other hypotheses have since emerged (19). For example, nonsteroidal anti-inflammatory drug–associated sodium/water retention may induce clinically relevant elevations in blood pressure (5). Could these effects be mitigated by the coadministration of aspirin, closer attention to blood pressure control, and/or lower doses or different regimens of celecoxib administration? Can the cardiovascular risks be predicted by genomic or proteomic assessments? Do any animal models currently used in chemoprevention drug development predict nonsteroidal anti-inflammatory drug–induced cardiovascular toxicities? What available biomarkers might predict cardiovascular toxicity? With regard to the clinical efficacy of celecoxib, questions relate to the key mechanism(s). Do animal models treated with celecoxib predict efficacy against adenomas, but not against colorectal cancer, or might we reasonably consider that longer durations of exposure would be effective against cancer as well? What pharmacodynamic biomarkers can be identified in animals that might serve as early predictors of clinical efficacy in humans? Do polymorphisms of key genes involved in the cellular signaling or metabolism of celecoxib dictate favorable or adverse responses in a given individual (20)?

In the area of population research, we might reasonably ask, now that COXIBs have been on the market for several years, whether similar cardiovascular risks occur in arthritis patients who typically use lower doses. If so, at what doses and when? Emerging data point to molecular commonalities among diverse diseases. Will meta-analyses or pooled analyses of data provide greater insights into potential cardiovascular toxicities? If not, what monitoring systems and data capturing systems might identify such risks earlier or without a placebo control in other cohorts? Does the celecoxib experience with cardiovascular toxicities suggest that regulatory agencies should consider large, postapproval, long-term trials of new drugs in an effort to identify ancillary clinical benefits and risks for other diseases? If the answer is yes, this opens up opportunities to mine information from disparate diseases and therapies and suggests how we might apply discovery and translational sciences in novel, multidisciplinary ways (21). Finally, we need to consider if, how, and when we should pool safety data from simultaneous trials, to identify potential risks earlier, and with greater reliability and accuracy.

Finally, in the clinical realm, the APC and PreSAP experiences suggest that we should consider offering chemopreventive trials of new agents to patients at much greater than average risk for cancer as a first approximation, in part, because they have more to gain than average-risk individuals. Combinations of agents should be considered earlier and more often, based on their profound promise in animal models (22, 23). In addition, whenever possible, we should try to confirm the efficacy of chemopreventive agents at the prespecified ''definitive'' time point and at an earlier time point as well. This approach could significantly accelerate progress and minimize the inherent risks of exposing participants to ineffective agents and/or unanticipated toxicities. In addition, we must recognize that the collection of tissues in a standardized, rigorous manner for subsequent translational investigations is essential for progress and must never be a secondary consideration. These translational investigations should yield a continuous stream of insights, even from productive failures, thus leveraging the public's investment in medical research.

In conclusion, the clinical successes and productive failures of the APC and PreSAP trials are stepping stones to progress. Although these trials may not achieve the intended immediate effect on medicine and public health (24), they are helping to fuel the next generation of translational research. Preventive oncology needs to prioritize and pursue effective agents, even those with suboptimal therapeutic indices. Without this commitment, progress will be slow. With it, we increase our rate of progress by expanding our research opportunities.

References

1. Zerhouni EA. Translational and clinical science—time for a new vision. N Engl J Med 2005;353:1621–3.
2. Arber N, Eagle CJ, Spicak J, et al. Celecoxib for the prevention of colorectal adenomatous polyps. N Engl J Med 2006;355:885–95.
3. Bertagnolli MM, Eagle CJ, Zauber AG, et al. Celecoxib for the prevention of sporadic colorectal adenomas. N Engl J Med 2006;355:873–84.
4. Solomon SD, McMurray JJ, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 2005;352:1071–80.
5. Solomon SD, Pfeffer MA, McMurray JJ, et al. Effect of celecoxib on cardiovascular events and blood pressure in two trials for the prevention of colorectal adenomas. Circulation 2006;114:1028–35.
6. Baron JA, Sandler RS, Bresalier RS, et al. A randomized trial of rofecoxib for the chemoprevention of colorectal adenomas. Gastroenterology 2006;131:1674–82.
7. Cannon CP, Curtis SP, FitzGerald GA, et al. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. Lancet 2006;368:1771–81.
8. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. JAMA 2006;296:1633–44.

9. Hawk ET, Viner J, Richmond E, Umar A. Non-steroidal anti-inflammatory drugs (NSAIDs) for colorectal cancer prevention. Cancer Chemother Biol Response Modif 2003;21:759–89.
10. Jacoby RF, Seibert K, Cole CE, Kelloff G, Lubet RA. The cyclooxygenase-2 inhibitor celecoxib is a potent preventive and therapeutic agent in the min mouse model of adenomatous polyposis. Cancer Res 2000;60:5040–4.
11. Reddy BS, Patlolla JM, Simi B, Wang SH, Rao CV. Prevention of colon cancer by low doses of celecoxib, a cyclooxygenase inhibitor, administered in diet rich in Ω-3 polyunsaturated fatty acids. Cancer Res 2005;65:8022–7.
12. Baron JA, Beach M, Mandel JS, et al. Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. N Engl J Med 1999;340:101–7.
13. Baron JA, Cole BF, Sandler RS, et al. A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med 2003;348:891–9.
14. Sandler RS, Halabi S, Baron JA, et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. N Engl J Med 2003;348:883–90.
15. Schatzkin A, Lanza E, Corle D, et al. Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. Polyp Prevention Trial Study Group. N Engl J Med 2000;342:1149–55.
16. Alberts DS, Martinez ME, Hess LM, et al. Phase III trial of ursodeoxycholic acid to prevent colorectal adenoma recurrence. J Natl Cancer Inst 2005;97:846–53.
17. Alberts DS, Martinez ME, Roe DJ, et al. Lack of effect of a high-fiber cereal supplement on the recurrence of colorectal adenomas. Phoenix Colon Cancer Prevention Physicians' Network. N Engl J Med 2000;342:1156–62.
18. Steinbach G, Lynch PM, Phillips RK, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med 2000;342:1946–52.
19. Grosser T, Fries S, FitzGerald GA. Biological basis for the cardiovascular consequences of COX-2 inhibition: therapeutic challenges and opportunities. J Clin Invest 2006;116:4–15.
20. Ulrich CM, Bigler J, Potter JD. Non-steroidal anti-inflammatory drugs for cancer prevention: promise, perils, and pharmacogenetics. Nat Rev Cancer 2006;6:130–40.
21. Butte AJ, Kohane IS. Creation and implications of a phenome-genome network. Nat Biotechnol 2006;24:55–62.
22. Nigro ND, Bull AW, Boyd ME. Inhibition of intestinal carcinogenesis in rats: effect of difluoromethylornithine with piroxicam or fish oil. J Natl Cancer Inst 1986;77:1309–13.
23. Reddy BS, Wang CX, Kong AN, et al. Prevention of azoxymethane-induced colon cancer by combination of low doses of atorvastatin, aspirin, and celecoxib in F 344 rats. Cancer Res 2006;66:4542–6.
24. Psaty BM, Potter JD. Risks and benefits of celecoxib to prevent recurrent adenomas. N Engl J Med 2006;355:950–2.