

COX-2 Inhibitors and Cancer

Key Points

- Celecoxib is a drug that blocks the production of prostaglandins (i.e., types of chemical messengers) by one of two cyclooxygenase (COX) enzymes. COX enzymes are turned on by the body in response to inflammation and by precancerous and cancerous tissues. Drugs that reduce pain and inflammation from many medical conditions (e.g., aspirin) inhibit both COX-1 and COX-2 enzymes (Question 3).
- In the Adenoma Prevention with Celecoxib (APC) Trial of more than 2,000 men and women age 30 and older, those on celecoxib were found to have 33 percent to 45 percent fewer new adenomas than those taking a placebo; however, those on celecoxib had almost twice the risk of a major cardiovascular event as people on placebo (Question 4).
- The National Cancer Institute continues to investigate celecoxib in ongoing clinical trials of patients at high risk for cancer due to strong laboratory, animal, epidemiologic, and clinical data showing the importance of the COX pathway in cancer (Question 11).

1. What are cyclooxygenase (COX) inhibitors?

Cyclooxygenase (COX) inhibitors are compounds that block the action of cyclooxygenase enzymes, which are produced in response to inflammation and by precancerous and cancerous tissues. Non-steroidal anti-inflammatory drugs (NSAIDs) reduce pain and inflammation from many medical conditions by inhibiting both of these enzymes (COX-1 and COX-2). NSAIDs that inhibit only COX-2 enzymes were created to allow people to have relief from pain and inflammation while reducing the chances of certain medical problems, such as stomach bleeding, that can occur when NSAIDs are taken regularly for long periods of time.



2. Why is the National Cancer Institute (NCI) studying COX inhibitors in cancer prevention and treatment?

More than a decade of epidemiologic research suggests that people who regularly take drugs that block COX enzymes have lower rates of certain precancers, cancers, and cancer-related deaths. The data are most consistent for colorectal cancer, but this reduction in risk is also seen for other cancers. Laboratory and animal studies using a variety of NSAIDs and COX-2 specific inhibitors show a decrease in cancer incidence with the use of these compounds. On a molecular level, studies have shown that the inhibition of the COX pathway changes the characteristics of cancer cells by reducing cell proliferation, increasing programmed cell death, reducing formation of blood vessels to feed cancer cells, and changing the body's immune response.

In addition, a laboratory study of colorectal cancer cells that do not produce COX-2, showed that treating these cells with celecoxib resulted in wide-ranging changes in protein production independent of COX-2. Following celecoxib treatment of these cells, researchers observed global changes in proteins involved in a variety of cellular functions, including metabolism, DNA and protein synthesis, protein folding, and the pattern of chemical decorations added to proteins. These results, published in the September 2006 issue of *Cancer Epidemiology Biomarkers and Prevention*, help explain the ability of celecoxib to prevent colorectal adenoma formation in the absence of COX-2 and could also potentially provide an explanation for the harmful effects of celecoxib observed when the drug is given at high doses.

3. What is celecoxib (Celebrex™)?

Celecoxib (Celebrex™) is a COX-2 inhibiting drug manufactured by Pfizer, Inc., New York. Celecoxib was approved by the U.S. Food and Drug Administration (FDA) for the treatment of both osteoarthritis and adult rheumatoid arthritis (diseases in which the joints are inflamed) in December 1998. Because scientific work suggested the potential for COX-2 inhibitors to prevent and treat cancer, the NCI, part of the National Institutes of Health (NIH), formed agreements with Pfizer to study this drug for the prevention and treatment of a variety of cancers.

4. What is the Adenoma Prevention with Celecoxib (APC) Trial?

The APC Trial was a clinical trial to determine if the arthritis drug celecoxib, which inhibits the enzyme COX-2, reduces the occurrence of new adenomas (precancerous polyps) in the colon and rectum of people who have already had such a polyp removed. More than 2,000 men and women age 30 and older were randomly assigned to take either 200 mg of celecoxib twice a day, 400 mg of celecoxib twice a day, or a placebo twice a day for three years. Participants taking celecoxib were found to have 33 percent to 45 percent fewer new adenomas than those taking a placebo. More than 90 centers, located mainly in the United States, but also in the United Kingdom, Australia, and Canada, took part in the trial. The trial enrolled participants from late 1999 through February 2002.

5. Why did NCI suspend the use of celecoxib in the Adenoma Prevention with Celecoxib (APC) Trial?

The use of celecoxib in the APC Trial was suspended on Dec. 17, 2004, because an initial analysis by an independent Data Safety and Monitoring Board (DSMB) showed that the risk of major fatal and non-fatal cardiovascular events (cardiovascular death, heart attack, stroke, or heart failure) was 2.5 times higher for participants taking the drug compared to those on a placebo. Investigators in the APC Trial immediately suspended study drug use, although the participants were observed for the planned remainder of the trial.

6. What did analysis of the cardiovascular events on the APC Trial show?

After the suspension of the trial in December 2004, an independent safety committee was established by NCI and the DSMBs of APC and another celecoxib study, Prevention of Spontaneous Adenomatous Polyps (PreSAP), to assess the cardiovascular risks caused by celecoxib in these two trials. In the APC Trial, the committee found that for patients taking 200 mg of celecoxib twice a day, the risk of cardiovascular death, heart attack, stroke, or heart failure increased 2.6 fold. The risk of these serious cardiovascular events increased 3.4 fold for patients taking 400 mg twice daily. PreSAP Trial participants took 400 mg of celecoxib once daily and experienced a slight (1.3 fold) but non-statistically significant increased risk of these adverse cardiovascular outcomes. The results were published in the August 31, 2006, issue of *Circulation: Journal of the American Heart Association*.

In the APC Trial placebo group, 7 of 679 people (1.0 percent) experienced a serious cardiovascular event, including one cardiovascular death. In the group of people taking 200 mg of celecoxib twice a day, 18 of 685 people (2.6 percent) had a serious cardiovascular event, including five cardiovascular deaths. In participants taking 400 mg of celecoxib twice a day, 23 of 671 people (3.4 percent) had a serious cardiovascular event, including six cardiovascular deaths. In the PreSAP Trial, 12 of 628 participants (1.9 percent) in the placebo group had a serious cardiovascular event, including four cardiovascular deaths. In PreSAP participants taking 400 mg once a day, 23 of 933 people (2.5 percent) experienced a serious cardiovascular event, including four cardiovascular deaths.

Participants in the APC Trial and the PreSAP Trial were allowed to take low-dose aspirin for cardiac protection (81 mg daily). Those who took low-dose aspirin had no different risk of serious cardiovascular events than those who did not take aspirin. However, the risk of a serious cardiovascular event was clearly higher in patients with a history of prior cardiovascular disease. In a combined analysis of the two trials, risk increased 1.8 fold for participants without cardiovascular event history and raised 2.3 fold for participants with a history of cardiovascular events.

7. Why did celecoxib increase the risk of these serious cardiovascular events?

The reason for the increased risk is not clear. An analysis of the cardiovascular events from the APC Trial published in *Circulation: Journal of the American Heart Association* showed that study participants taking celecoxib had a significant increase in their blood pressure, which may have affected their heart disease risk. Researchers are working to understand the possible mechanisms so they may one day be able to determine who is at risk for these serious cardiovascular events and who might be able to take the drug safely. Researchers may investigate giving lower doses of celecoxib or different dose regimens (giving once instead of twice a day) to determine if this causes less cardiovascular risk while still providing pain relief or polyp prevention.

8. What did NCI do to notify patients on COX-2 inhibitor clinical trials about this risk for serious cardiovascular events?

NCI notified all of the principal investigators of its sponsored trials involving COX-2 inhibitors about the increased cardiovascular risk seen in the APC Trial. The principal investigators were instructed to notify their institutional review boards (IRBs), data safety monitoring boards (DSMBs), and trial participants about this new information. NCI also required that the informed consent for these trials be revised to reflect this new information and that participants in the trials be re-consented (that is, asked to sign new consent forms with updated information about the risks and benefits of the trials).

9. What language was added to the informed consent for these trials?

As recommended by NCI, the following language was added to revised informed consent forms: “Recently, an increased risk of heart attacks, strokes, and/or deaths resulting from heart or blood vessel disease has been reported among people taking celecoxib in clinical studies. Although the increased risk is two to three times greater than the risk of patients who did not take celecoxib, these serious adverse events are rare. Taking celecoxib may increase your risk of one of these events.”

10. How many clinical trials were affected by this information? Were any trials closed?

As of December 2004, NCI had about 50 prevention and treatment clinical trials with celecoxib of varying sizes, either open or in planning stages. The 26 prevention trials ranged in size from under 10 participants to more than 2,000 participants and were for the prevention of bladder, breast, cervical, colorectal, esophageal, head and neck, skin, lung, oral, and prostate cancers, as well as multiple myeloma. NCI collaborated with Pfizer on the majority of the large prevention trials. The 23 treatment trials were mostly small phase I or II clinical trials in cancers including pancreatic, breast, ovarian, non-small cell lung, and other solid tumors. The treatment trials included two randomized, phase III clinical trials in women with breast cancer.

NCI did not close any trials, but required that the PIs notify their IRBs, DSMBs, and participants of the new information. In response to the new information, the PIs, IRBs, and DSMBs had to consider the risks and benefits of continuing each trial, including both ethical and practical issues. For instance, some trials were close to completion and the PIs chose not to continue the intervention and to move to analyze the data at that point. For many treatment trials, celecoxib was not the primary treatment being used, nor was its effectiveness the primary objective of the trial; for these studies, celecoxib was discontinued. Other trials, in which the duration or dosage of celecoxib was short or low, and the cohort was at increased risk for cancer, continued as they were designed.

NCI continues to test celecoxib in 18 clinical trials for prevention and one clinical trial for treatment, as well as in numerous laboratory studies.

11. What other NCI-supported analyses are under way to better understand the potential risks of taking celecoxib?

A panel of NCI-sponsored investigators is assessing the cardiovascular and cerebrovascular safety of celecoxib using data from six randomized, placebo-controlled trials testing celecoxib. Use of celecoxib was nearly complete, suspended, or dropped in all of these trials. By analyzing the cardiovascular and cerebrovascular safety data from these studies (and using consistent definitions of these events), a clearer picture of the risk profile of celecoxib may emerge. Analysis is ongoing and completion is expected in late 2006.

This safety analysis includes data from:

- Three trials sponsored by NCI
 - The Adenoma Prevention with Celecoxib Trial, a study of men and women with a prior colorectal adenoma.
 - The SelCel trial, a study of men and women with a prior colorectal adenoma.
 - The MA27 Breast Adjuvant Trial, a study of postmenopausal women with estrogen receptor-positive breast cancer.
- Two trials sponsored by other institutes at the NIH
 - The National Institute on Aging's ADAPT trial, which includes men and women at risk for Alzheimer's disease.
 - The National Eye Institute's Diabetic Retinopathy Trial of people with diabetes and diabetic macular edema.
- Pfizer-sponsored Pre-SAP trial of men and women with a prior colorectal adenoma.

12. Should people continue to use celecoxib for pain relief?

The average dose of celecoxib used for pain relief in osteoarthritis and adult rheumatoid arthritis patients, 200 mg once a day, is less than all doses studied in the APC and PreSAP trials. Therefore, it is unknown if the cardiovascular risks seen in these trials of higher doses apply to the use of celecoxib at lower doses in these patients. The FDA has advice for consumers and physicians regarding pain relievers and celecoxib on its Web site at <http://www.fda.gov> on the Internet.

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Related NCI materials and Web pages:

- National Cancer Institute Fact Sheet 2.11, *Clinical Trials* (<http://www.cancer.gov/cancertopics/factsheet/Information/clinical-trials>)
- Colon and Rectal Cancer Home Page (<http://www.cancer.gov/cancertopics/types/colon-and-rectal>)

How can we help?

We offer comprehensive research-based information for patients and their families, health professionals, cancer researchers, advocates, and the public.

- **Call** NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237)
- **Visit** us at <http://www.cancer.gov> or <http://www.cancer.gov/espanol>
- **Chat** using LiveHelp, NCI's instant messaging service, at <http://www.cancer.gov/livehelp>
- **E-mail** us at cancergovstaff@mail.nih.gov
- **Order** publications at <http://www.cancer.gov/publications> or by calling 1-800-4-CANCER
- **Get help** with quitting smoking at 1-877-44U-QUIT (1-877-448-7848)

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