



Patient Report

The COX-2 Trail

A Report by
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As usual, I am approaching scientific, medical and other literature from a patient-view. My hope in this and other reports is to examine and interpret the literature from the perspective of a PJS patient. I am most interested in the people with PJS, our freedom and well-being. COX-2 and its inhibition are big news that affects us. Hopefully this overview report will provide some background on these topics.

Introduction to COX-2

The COX-2 inhibitors, Celebrex (celecoxib)¹ and Vioxx (rofecoxib)² are anti-inflammatory medications currently used in treating osteoarthritis, rheumatoid arthritis and other chronic pain. These medications were developed because earlier painkillers, the NSAIDs or non-steroidal anti-inflammatory drugs like aspirin often led to GI bleeding and ulcers. The NSAIDs are composed of both Cox-1 and COX-2 inhibitors. It seems that Cox-1 inhibition increases ulcer risk, while COX-2 inhibition doesn't.

During the past four years research has indicated that there is increased COX-2 expression in different cancers. There are now theories that COX-2 inhibitors may influence the development and treatment of cancer and polyps.

“The National Cancer Institute's Division of Cancer Prevention is studying Celebrex™ for the prevention of cancer in people with precancerous conditions and in people at high risk for recurring cancer NCI is collaborating with Pharmacia Corporation of Peapack, New Jersey, the makers of Celebrex™, and Pfizer Incorporated in New York, New York... To date there are 1,549 subjects randomized. Prospective study participants should contact the Columbia Presbyterian Medical Center directly at 212-305-3224.”³

COX-2 expression in cancer and polyps

There are many reports in the medical literature that COX-2 expression correlates with cancer aggressiveness. Tumor size, differentiation, invasion, proliferation, vascularization, recurrence, metastasis and high grade tumors have an elevated expression of COX-2. Additionally, NSAID use seems to reduce the incidence of a variety of cancers including colorectal, breast and pancreatic cancers.⁴

And there have been small, preliminary studies that NSAIDs and COX-2 inhibitors reduce the polyps in FAP. In a six-month study, FAP polyps were reduced by 14.5%.⁵ And a longer study of 12 patients showed success showed that “prolonged use of sulindac appeared effective in decreasing polyp number and in preventing recurrence of higher-grade adenomas in the retained rectal segment of most FAP patients with IRA.”⁶ But a randomized double-blind placebo-controlled study of 41 subjects revealed that four years of treatment with the NSAID sulindac did not slow the development of adenomas, or decrease the number or size of polyps in mutant APC carriers. Adenomas developed in 43% of the sulindac-treated group, and 55% of the placebo group — not a statistically significant difference. The authors propose that the lack of efficacy might have been due to the development of resistance to sulindac.⁷

COX-2 inhibitors seem like solution to both COX-2 overexpression in cancer and the limits of NSAIDS.

“Pharmacia is running up against an old engineering axiom: When you only have a hammer, every problem starts to look like a nail. The drug giant is hoping to use its sole blockbuster, the arthritis treatment Celebrex, to treat and prevent cancer. So far, experiments that use Celebrex to fight cancerous and pre-cancerous growths are promising.”⁸

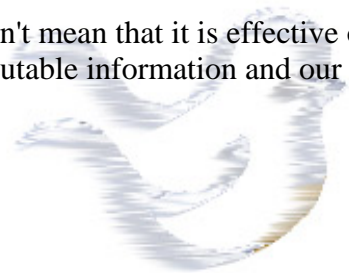
COX-2 inhibitors in chronic pain

Why are COX-2 inhibitors so successful? Celebrex was the #10 selling drug in the USA in 2001. In the USA each year over 13 million people use NSAIDs regularly, 30 billion over-the-counter NSAID tablets are sold annually, and 70 million NSAID prescriptions are written. There is a cost for all this pain relief. NSAIDs have over 100 side effects, of which gastrointestinal toxicity is the most common. Amid long-term users of NSAIDs, the mortality rate from GI complications is 0.22 percent per year. NSAID-related GI complications rank 15th among most common causes of death in the USA. NSAID-induced diseases cause more than 100,000 hospitalizations per year, at an estimated cost of \$15,000 each. The annual expenditure for treatment of these GI complications runs around \$2 billion.⁹

Most NSAIDs are self prescribed, i.e., sold over-the counter. The COX-2 inhibitors require a prescription. If NSAIDs with their high rate of problems are deemed safe enough for self-prescription, I wonder why the "safer" COX-2 inhibitors require doctor prescription. Also, the FDA approved them for long-term pain relief, but not for acute pain.

Not only are doctors sold the benefits of these drugs, but patients in the USA and New Zealand receive advertisements about their benefits.¹⁰ These advertisements are in magazines and television and usually show a happy, active person stating that their problems have been solved by this drug or that. Beyond the advertisements to physicians and patients, many drug companies mount multi-prong campaigns to promote the "need" for new drugs or treatments. These campaigns use ersatz or co-opted consumer groups, news stories, websites and advertising to physicians and patients.¹¹ This is especially true of campaigns by top-selling pharmaceutical companies.

But just because a drug is heavily advertised and used doesn't mean that it is effective or ineffective, safe or unsafe. We must rely upon tests and trials, reputable information and our own experiences to determine safety and efficacy.



A new application for a proven drug?

“Scientists are hard at work recycling Celebrex and Vioxx, the red-hot inflammation pills taken by tens of millions for arthritis. They have an unlikely new use in mind, one maybe even more important than soothing throbbing joints. Their goal: prove these medicines prevent cancer and perhaps even help cure it. While there are good scientific reasons to think they are onto something, the experiments to settle it are not finished, and the optimists may be dead wrong. Nevertheless, cancer researchers and pharmaceutical executives entertain fantasies of a breakthrough role for an off-the-shelf medicine.”¹²

Several long searches in PubMed and medical textbooks revealed that though COX-2 is overexpressed in cancers, especially nasty cancers, it is unclear why or what the role of COX-2 is in cancer development. Perhaps it indicates that the body is fighting especially hard against the cancer. Or that this cancer has progressed further than another. I found no proof that COX-2 causes cancer or that its inhibition would prevent cancer. The quote above contains the words unlikely, maybe and entertain fantasies. The Forbes article quoted below wasn't even so polite.

“Several things could still prevent the drug from making the leap from killing pain to treating cancer. There is no conclusive proof that Celebrex works as a preventive drug for anything other than a rare genetic condition that can lead to colorectal cancer. Additionally, sales of Celebrex and similar painkillers known as COX-2 inhibitors have been hurt by concerns that they might cause heart problems. Vioxx, a COX-2 made by Merck, had cardiac precautionary language added to its label.”⁸

COX-2 inhibitor safety

“Treatment of musculoskeletal pain should focus on the underlying cause, and in many cases the use of any anti-inflammatory drug is inappropriate. For non-inflammatory musculoskeletal pain, acetaminophen remains the drug of choice, and nonpharmacologic treatments including strengthening and stretching exercises, ice or heat are often underused. If COX-2 inhibitors are indicated, patients should be informed of the risks and benefits specific to each drug.”¹³

The BMJ printed a fascinating criticism of the COX-2 CLASS trial in their June 1, 2002 edition.¹⁴ The authors alleged the study funded by celecoxib's manufacturer Pharmacia had many flaws and omissions. “Publishing and distributing overoptimistic, short term data using post hoc changes to the protocol, while omitting disappointing long term data of two trials which involved large numbers of volunteers is misleading.” Additionally, “the flawed findings published in the original article¹⁵ appear to be widely distributed and believed. About 30,000 reprints of CLASS were bought from the publisher (W Barlotta, personal communication) and a recent search of the Science Citation Index yielded 169 articles citing it, more than 10 times as many citations as for any other article published in the same issue. This wide distribution and citation has coincided with the sales of celecoxib increasing from \$2623m in 2000 to \$3114m in 2001.”¹⁴

So what if the pivotal celecoxib study was flawed? If Celebrex is the #10 prescribed drug with sales of over 3 billion dollars annually, it must be safe? Well, sort of. Actually Google searches for COX-2 inhibitors netted more websites of attorneys seeking clients for COX-2 law suits, than scientific articles about the safety and effectiveness of this drug -- for pain use OR cancer prevention. I'm not sure the lawyers are right either, but find it interesting that they are circling around COX-2 inhibitors. You might want to visit some of these sites, including the Google top-rated site www.cox2infocenter.com because they contain links to information critical of COX-2 inhibitors.

The book titled **Worst Pills, Best Pills** has an entry on celecoxib titled *Do Not Use Until February 2004: Celecoxib (CELEBREX) - Another Nonsteroidal Anti-Inflammatory Drug (NSAID)*. There are many criticisms and concerns about the drug with the conclusion, "We recommend that you should always wait at least five years from the date of release to take any new drug unless it is one of those rare 'breakthrough' drugs that offers a documented therapeutic advantage over older, proven drugs. New drugs are tested in a relatively small number of people before being approved, and serious adverse effects or life-threatening drug interactions may not be detected until the new drug has been taken by hundreds of thousands of people. A number of new drugs have been withdrawn usually within five years after a drug's release. Also, serious new adverse reaction warnings have been added to the labeling of a number of drugs, or new interactions have been detected, usually within five years after a drug's release. ...You should wait at least five years to take celecoxib. It is an expensive new drug that may be no more effective and no safer than acetaminophen or older NSAIDs at a fraction of the cost."¹⁶

For more information on possible side effects, consult the **Physicians' Desk Reference**.^{1,2}

Of course people with PJS polyps and related cancer might not want to wait five years before trying COX-2 inhibitors. I suggest finding a good clinical trial to join.



¹www.gettingwell.com/drug_info/rxdrugprofiles/drugs/CEL1078.shtml

²www.gettingwell.com/drug_info/rxdrugprofiles/drugs/VIO1533.shtml

³Press release *Popular Arthritic Medication May Prevent Colon Cancer, Prevention of Colon Cancer Focus of Columbia Presbyterian Medical Center Study*.
www.nyp.org/news/2002/2.19.2002.html

⁴Wallace, Jeanne. *Nutritional and Botanical Modulation of the Inflammatory Cascade - Eicosanoids, Cyclooxygenases, and Lipoxygenases- As an Adjunct in Cancer Therapy*. Integrative Cancer Therapies 1(1); 2002:7

⁵Phillips RK, Wallace MH, Lynch PM, Hawk E, Gordon GB, Saunders BP, Wakabayashi N, Shen Y, Zimmerman S, Godio L, Rodrigues-Bigas M, Su LK, Sherman J, Kelloff G, Levin B, Steinbach G. FAP Study Group. *A randomised, double blind, placebo controlled study of celecoxib, a selective cyclooxygenase 2 inhibitor, on duodenal polyposis in familial adenomatous polyposis*. Gut 2002 Jun;50(6):857-60

⁶Cruz-Correa M, Hyland LM, Romans KE, Booker SV, Giardiello FM. *What is the long-term effectiveness of the nonsteroidal anti-inflammatory drug (NSAID), sulindac, in reducing adenomas in the retained rectal segments of patients with familial adenomatous polyposis (FAP)?* Gastroenterology. 2002;122(3):641-645

⁷Giardiello, F. M. *Primary chemoprevention of familial adenomatous polyposis with sulindac*. N. Engl. J. Med. 346, 1054–1059 (2002)

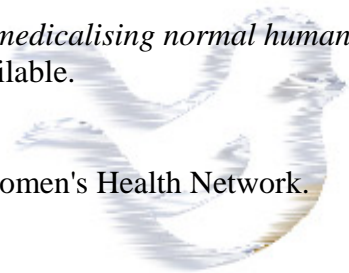
⁸www.forbes.com/2002/04/25/0425celebrex.html

⁹Wolfe MM, Lichtenstein DR, Singh G. *Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs*. N Engl J Med. 1999 Jun 17;340(24):1888-99. Review. No abstract available.
PMID: 10369853 [PubMed - indexed for MEDLINE]

¹⁰Mintzes B. *For and against: Direct to consumer advertising is medicalising normal human experience*. BMJ. 2002 Apr 13;324(7342):908-9. No abstract available.
PMID: 11950745 [PubMed - indexed for MEDLINE]

¹¹*Manufacturing Need, Manufacturing "Knowledge"*. National Women's Health Network. May/June 2002 :1-4. www.womenshealthnetwork.org

¹²*Widely used arthritis pills may be new treatment for cancer*. Cancer Weekly. April 23, 2002. NewsRx.com



¹³ Wooltorton, Eric. *What's all the fuss? Safety concerns about COX-2 inhibitors rofecoxib (Vioxx) and celecoxib (Celebrex)*. CMAJ: Canadian Medical Association Journal. 6/25/2002. Vol. 166, Issue 13, p1692, 2p, 1 graph

¹⁴ Juni P, Rutjes AW, Dieppe PA. *Are selective COX 2 inhibitors superior to traditional non steroidal anti-inflammatory drugs?* BMJ. 2002 Jun 1;324(7349):1287-8. No abstract available. PMID: 12039807 [PubMed - indexed for MEDLINE]

¹⁵ Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, Makuch R, Eisen G, Agrawal NM, Stenson WF, Burr AM, Zhao WW, Kent JD, Lefkowitz JB, Verburg KM, Geis GS. *Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study*. JAMA. 2000 Sep 13;284(10):1247-55. PMID: 10979111 [PubMed - indexed for MEDLINE]

¹⁶ www.citizen.org/publications/release.cfm?ID=5069

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