Emerging options with coxib therapy

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ABSTRACT

Future clinical applications of cyclooxygenase (COX)-2–selective inhibitors (coxibs) are likely to extend beyond their current use as oral analgesics in high-risk arthritis patients. The clinical utility of coxibs for the treatment of Alzheimer's disease (AD) is under investigation. Epidemiological surveys, preclinical studies, and preliminary clinical trials with nonsteroidal anti-inflammatory drugs (NSAIDs) have suggested that inflammatory mechanisms play a role in the neurodegeneration of AD. Clinical trials are currently being conducted to determine the effect of coxibs on the rate of AD progression. The use of coxibs as chemopreventive agents in colorectal cancer (CRC) is also under investigation. The chemopreventive benefits of coxibs to promote cell death (apoptosis) and inhibit angiogenesis in CRC have been shown in tumor cell lines and in animal and human models. In addition, palliative care clinicians and oncologists are increasingly including coxibs in their management of cancer pain. Coxibs are utilized for their opioid-sparing effect in the management of cancer pain, without impairing wound healing, or promoting bleeding diathesis (antiplatelet effects) or adverse gastrointestinal effects in patients receiving chemotherapy or radiation treatment.

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Disclosure. The author has indicated that he has been a consultant for Merck and Purdue and is on the speakers' bureaus of Merck and Purdue.

As the size of the aging population increases, primary care physicians, who practice at the front line of medical care, can expect to see more patients with Alzheimer's disease (AD) or colorectal cancer (CRC) in their clinical practice.[1–4] Perhaps surprisingly, cyclooxygenase (COX)-2–selective inhibitors (coxibs) may have a role in treating these diseases in addition to their established utility in the management of arthritis and other painful conditions.

AD is an age-related neurological disorder leading to progressive dementia. The number of patients in the United States with primary dementia (AD and vascular dementia) is approximately 4 million, and an estimated 100,000 new patients are expected to be diagnosed each year.[5] Slowing or preventing the neurodegenerative process in AD is one of the major challenges facing healthcare professionals today.[6]

Similarly, the risk of developing CRC grows with advancing age. The American Cancer Society estimates that in 2001 approximately 135,400 new cases of CRC will have been diagnosed and 56,700 Americans will have died from CRC.[4] While risk-minimization recommendations exist,[4,7] researchers continue to search for an effective agent that could prevent or limit the progression of CRC.

Another area of clinical concern is the control of malignant pain associated with cancer, a primary clinical objective when caring for cancer patients. The role of primary care physicians is essential in preserving patients' quality of life, as they can coordinate treatment and patient evaluation with oncologists and palliative care clinicians.[8] Strategies uti-

lizing nonsteroidal anti-inflammatory drugs (NSAIDs), alone or in association with an opioid, can effectively manage most cancer pain. However, their use is limited by side effects typically associated with NSAID therapy.

The clinical benefits of coxibs for the treatment of AD and chemoprevention of CRC are being evaluated as a result of an increased understanding of the pathophysiology of both AD and CRC. The unique pharmacology of coxibs has already demonstrated potential value in these areas, in addition to their use in the management of cancer pain. This article will review the potential COX-2–related therapeutic targets that have been revealed in these diseases and that may offer unique treatment options for sufferers and physicians alike.

■ ALZHEIMER'S DISEASE

A loss of neuronal function, most likely in glutamatergic neurons in neocortical and hypothalamic structures, is believed to be responsible for the signs and symptoms of AD.[6,9–12] The etiology of AD is not fully understood, but three interactive developments—senile plaques, neurofibrillary tangles, and inflammation—have been identified as pathogenic factors.[10,11] Notably, markers of local inflammation, such as activated microglia, reactive astrocytes, complement proteins, cytokines, and reactive mediators of oxygen and nitrogen (free radicals), all occur in close proximity to senile plaques and neurofibrillary tangles containing beta-amyloid (Aβ) and tau (τ) proteins.[9–11] Furthermore, senile plaques associated with activated complement factors, activated microglia, and reactive astrocytes—without any apparent influx of leukocytes—are strongly suggestive of a locally-induced, nonimmune-mediated inflammatory response.[9,10]

Inflammation in Alzheimer's disease

The inflammatory hypothesis of AD suggests that these inflammatory processes either directly or indirectly promote neurotoxicity and neurodegeneration.[11–15] The markers of a neuroinflammatory response detected in AD brain tissue represent a protective reaction to neuronal stress, but most likely contribute to neuronal stress as well.[9,11] One pharmacologic approach to retard AD progression, therefore, would be to suppress inflammation with anti-inflammatory treatment using nonselective NSAIDs or the COX-2–selective inhibitors.[6,9]

Epidemiological surveys have proven to be quite useful in investigating the pathogenesis of AD since circumstances associated with a decreased prevalence of disease may help to identify factors that may be providing a protective influence.[11] Several epidemiological surveys have identified chronic exposure to an anti-inflammatory agent as a protective factor for the development of AD.

Understanding the evidence

The first line of epidemiological inquiry entailed case-controlled studies of medical parameters in individuals diagnosed with AD.[16–23] In all but one of seven studies,[16] a lower prevalence of concomitant arthritis was consistently identified as a "protective" factor against AD.

Cross-sectional surveys of elderly individuals have measured the prevalence of concurrent diagnoses of AD and rheumatoid arthritis (RA), a disease typically managed by chronic anti-inflammatory treatments. Three large, population-based surveys all found a significantly lower prevalence of AD among patients with RA, providing some evidence of a positive benefit conferred by anti-inflammatory treatment.[14,24,25] Two smaller studies gave somewhat conflicting results. One study showed a significantly lower prevalence of RA among a cohort of patients with AD compared with the prevalence of RA in a cognitively intact cohort (2% vs 13%; odds ratio [OR] = 0.17; $P < .005$).[23,26] The second study reported no difference in the prevalence of RA among patients with AD than in those who were cognitively intact (6% vs 4%; OR = 1.18; 95% confidence interval [CI], 0.35–3.91).[23,27]

The impact of chronic exposure to steroid therapy on the development of AD has also been reviewed in epidemiological studies. Four case-control studies all found that exposure to steroid treatment provided a protective effect, if not as numerically large an effect as seen in studies evaluating the impact of a diagnosis of arthritis or RA.[20–23,27]

Bestowing a bit more favor on the inflammatory hypothesis of AD and the putative role for COX-2–selective inhibitors are results from studies that found a protective effect with NSAID use on the development of AD.[20–22] Notably, the overall OR for these studies was 0.50 (95% CI, 0.34–0.72; $P = .0002$), compared with that for those studies evaluating the impact of steroid therapy (0.66; 95% CI 0.43–1.00; $P = .049$). These data suggest that NSAID use (which *directly* targets COX activity as

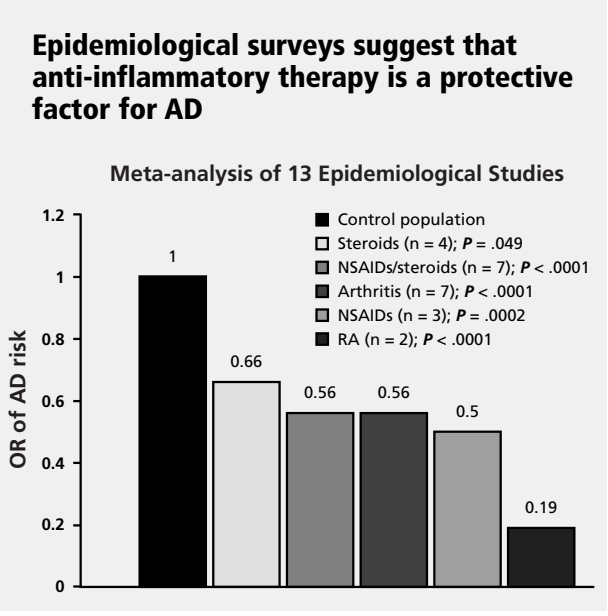

FIGURE 1. A meta-analysis of 13 epidemiological surveys suggests that prolonged exposure to an anti-inflammatory treatment confers a protective influence on the development of AD. Whether the variable was a diagnosis of arthritis or RA, or anti-inflammatory treatment with a steroid, NSAID, or both, the OR of a concomitant diagnosis of AD was well below 1.0. The greatest protection appears to occur in individuals with RA. This may be explained by the fact that the anti-inflammatory dose for NSAIDs required to control RA is higher than the dose for analgesia.[23]

contrasted to steroids, which act on the acute phase of the inflammatory response) confers a greater degree of protection against the development of AD than does steroid exposure.[20,22,23]

A comparable level of protection with NSAID use was seen in two population-based surveys. In one, the prevalence of NSAID users in the population of two AD clinical trials was 0.5% compared with a 22% prevalence of NSAID users in a control cohort from three surveys of elderly patients.[23,28] In the second population-based survey, 1.4% of 365 NSAID users were found to have AD compared with 2.5% in a cohort of 5,893 institutionalized and community-living individuals over 55 years of age.[29]

A third population-based study, the Baltimore Longitudinal Study on Aging (BLSA), followed 1,686 individuals prospectively to evaluate the effect of analgesic agents on the risk of AD.[30] With less than 2 years of nonaspirin NSAID use, the relative risk (RR) was 0.65 (95% CI, 0.33–1.29), and with 2 years or more of nonaspirin NSAID use, the RR dropped to 0.40 (95% CI, 0.19–0.84). Less benefit was seen with low-dose aspirin use: the RR was 0.74 (95% CI, 0.46–1.18). No benefit was seen with acetaminophen use, which has no anti-inflammatory properties: the RR was 1.35 (95% CI, 0.79–2.30).[30]

Another longitudinal survey was conducted at The Johns Hopkins Alzheimer's Disease Research Clinic. Among 209 patients entering the research clinic, only 15% claimed prior or current NSAID use.[31] During a 1-year period, the 32 NSAID users experienced later onset, reduced severity, and slower progression of AD symptoms when compared with age-matched and disease duration-matched patients not taking an NSAID.[23,31]

Anti-inflammatory treatment of AD

Based on these findings, several clinical trials were conducted to determine whether anti-inflammatory treatment could slow or prevent AD progression (**Figure 1**). Indomethacin, a COX-1 preferential inhibitor, was the first anti-inflammatory agent reported to have possible beneficial action in patients with probable AD (Mini-Mental Status Examination [MMSE] score of at least 16). In a small double-blind trial (n = 44), participants who received either indomethacin (100–150 mg/day) or placebo during a 6-month period experienced a 1.3% *improvement* or 8.4% *worsening* in AD symptoms, respectively; the placebo group demonstrated a typical rate of AD progression. However, five (21%) of the indomethacin-treated patients withdrew as a result of gastrointestinal (GI) adverse events, attesting to the limitations of chronic indomethacin treatment, especially in elderly patients.[32] In addition to indomethacin's adverse GI safety profile, clinicians have reported an increase in delirium or agitated behavior in their AD patients treated with indomethacin.[33–35]

Another small placebo-controlled trial evaluated diclofenac in patients with mild-to-moderate AD (MMSE score between 11 and 25). Patients treated with diclofenac 50 mg plus misoprostol 200 μg for 25 weeks were evaluated by both Alzheimer Disease Assessment Scale–cognitive (ADAS-cog) and ADAS-noncognitive scales. While not statistically significant, some observed trends suggested that the placebo group deteriorated to a greater degree than the treated group. Furthermore, the number of withdrawals due to drug-related adverse events was greater in the treatment group—50% compared

with 12% in the placebo group.[36]

In contrast to these preliminary findings with nonselective NSAIDs, no beneficial action of the steroid prednisone has been demonstrated. In one randomized, placebo-controlled multicenter trial of low-dose prednisone (10 mg/day for 1 year), 138 patients with probable AD had equivalent ADAS-cog mean scores regardless of treatment arm.[37]

Overall, these findings suggest NSAIDs but not steroids may slow AD progression, and that the antidementia activity of anti-inflammatory agents may be attributed to inhibition of prostaglandin production mediated by COX isozymes. While all NSAIDs, to one degree or another, nonselectively inhibit COX, the COX-2–selective inhibitors spare the constitutive COX-1 isozyme. By primarily targeting the inducible COX-2 isozyme, inflammation mediated by the proinflammatory prostaglandins is ameliorated.[12,38]

COX isoenzymes, coxibs, and Alzheimer's disease

The distinction between COX isozymes is not as well defined in the brain, however. Immunohistochemistry and mRNA-probe studies have found that in the normal brain, both COX-1 and COX-2 are constitutively expressed in all areas examined.[39] Some differential expression may exist, as COX-1 expression was detected in microglial cells whereas COX-2 was found in glutamatergic neurons; no COX expression was detected in astrocytes.[9,10,39,40] In AD frontal cortex, COX-2 expression is upregulated 25% over levels in normal brain, whereas COX-1 expression is decreased 10% to 15%.[39,41]

Studies have shown that COX-2 expression can be rapidly induced by nerve cell injury, tumor promoters, bacterial endotoxins, neurotoxins, cytokines, and anoxia, as well as by noninflammatory triggers such as neuronal stimulation, growth factors, and hormones.[10,39,42] Neuronal upregulation of COX-2 may be both protective as well as a pathogenic response in AD.[9,10,39]

Clinical trials of coxib therapy in AD may provide some answers. A recent 1-year trial with celecoxib (200 mg BID) was conducted in 425 patients with probable AD.[10,43] Although celecoxib was well tolerated, there was no difference between the two groups in their rates of disease progression, as measured by ADAS-cog and Clinician's Interview-Based Impression of Change (CIBIC-plus) scores.

The Alzheimer's Disease Cooperative Study (ADCS), a National Institute of Aging–sponsored consortium, is conducting a clinical trial with rofecoxib. This 1-year, three-arm study is being conducted in 330 patients with probable AD. Study treatments are rofecoxib 25 mg once daily, naproxen 200 mg twice daily, or placebo, and the primary outcome is a mean change in status measured by ADAS-cog. Results of the data analysis are expected in early 2002.

■ COLORECTAL CANCER

Evidence suggests that NSAIDs can prevent the development of CRC.[44] CRC is the second leading cause of cancer-related mortalities in the United States, approximately 57,000 in 1999.[4,45] In the United States, 93% of all CRC cases occur in patients over 50 years of age, and the 5-year survival rate for patients with CRC is approximately 60%.[46] Worldwide, CRC accounts for approximately 556,000 mortalities.

Familial adenomatous polyposis (FAP) is a condition considered to be a precursor to CRC.[47,48] It is a rare condition caused by a defect in the gene *APC* (adenomatous polyposis coli), normally a tumor suppressor, that predisposes one to develop hundreds of colonic polyps. If left untreated, polyps can lead to colon cancer.[49]

Familial adenomatous polyposis, colorectal cancer, and COX

COX-2 is believed to play a role in the development of FAP and CRC. While COX-1 is constitutively expressed in normal GI mucosa, the level of COX-2 is low or undetectable.[50–52] In animal models of FAP or CRC, however, increased expression of COX-2 has been demonstrated.

One study was conducted in multiple intestinal neoplasia (*MIN*) mice, a model for FAP in humans. In adenomas harvested from *MIN* mouse intestine, the levels of COX-2 mRNA and protein were approximately threefold higher than levels of COX-2 in normal mucosa from the same mouse. These findings implicate COX-2 expression at an early, preinvasive stage of CRC.[50] A second study with rats found increased levels of COX-2, but not COX-1, mRNA and protein in colon tumors that developed following treatment with a colorectal carcinogen.[51]

The same differential expression of the COX isozymes has been detected in human colorectal neoplasia. For example, 86% of tumor samples har-

vested from patients with CRC contained greater levels of COX-2 mRNA relative to those in the same patient's noncancerous mucosa. In 43% of the colorectal adenomas examined, an increase in COX-2 gene expression was also detected, again showing upregulation at an early stage in colorectal carcinogenesis. However, the level of COX-1 mRNA in all carcinomas examined was equivalent to the level seen in normal mucosa.[52]

COX-2, NSAIDs, apoptosis, and tumorigenesis

Apoptosis, or programmed cell death, is an active process that removes mutated or damaged cells, thus contributing to the prevention of cancer development. Disruptions in apoptosis and COX-2–mediated processes may provide some explanation for the promotion of colorectal tumor formation by COX-2 upregulation.

Briefly, upregulation of COX-2 results in decreased levels of the COX substrate, arachidonic acid (AA), and simultaneously, increased production of COX-mediated eicosanoids.[52,53] COX-2–mediated prostaglandins stimulate cell proliferation, and other COX-2–mediated factors regulate tumor angiogenesis (tumor growth beyond 2 to 3 mm in size is dependent on tumor angiogenesis).[52–54] Loss of constraint of tumor cell growth is thought to result from decreases in AA, which ultimately result in lower levels of ceramide, a potent inducer of apoptosis.[55] (AA stimulates sphingomyelinase activity to catalyze the conversion of sphingomyelin to ceramide.)

Recent in vitro studies have implicated a key role of COX-2 in mediating mitogenic growth factor signaling and in the downregulation of apoptosis in human colon cancer cell lines.[48] Notably, NSAIDs have been shown to reverse this COX-2 effect in human colon cancer cell lines, promoting apoptosis. In one study, cancer cells were treated with the nonselective NSAID sulindac or its active metabolite, sulindac sulfide. Only sulindac sulfide resulted in dose-dependent apoptosis, which was not reversed by exogenous prostaglandin E_2 (PGE_2), the major eicosanoid in colon tumors, or by other prostaglandins. Furthermore, exogenous AA, but not a control fatty acid, was a potent inducer of apoptosis, presumably due to increased levels of ceramide. In this experimental model, sulindac sulfide treatment elevated ceramide levels tenfold relative to untreated cells. A synergistic effect on apoptosis was seen when sulindac sulfide and AA were combined.[55]

Similar effects were seen with indomethacin, which also displays tumor-suppressive activity in intestinal epithelial cells. In indomethacin-treated cells, there was a three- to four-fold increase in AA and a six-fold increase in ceramide; 94% of the treated cells underwent apoptosis.[55]

An in vitro study with the coxib SC58125 found increased rates of apoptosis in a human colon-cancer cell line that maintains high constitutive COX-2 expression and prostaglandin production.[56]

Tumor-related angiogenesis mostly relies on tumor cell expression of angiogenic factors and endothelial tube formation. The role of COX inhibition on these processes was investigated in an in vitro model of tumor angiogenesis. Endothelial cells and colon carcinoma cells engineered to differentially express COX-1 and/or COX-2 were co-cultured and exposed to aspirin or to NS-398, a COX-2–selective inhibitor. Inhibition of COX-2 activity by either agent reduced tumor cell production of angiogenic factors. However, aspirin or a COX-1 antisense oligonucleotide, but not NS-398 or a COX-2 antisense oligonucleotide, inhibited endothelial tube formation. Furthermore, tumor cell expression of angiogenic factors resulted in upregulated endothelial cell expression of COX-1. These results suggest that NSAIDs may inhibit angiogenesis by two mechanisms: inhibition of COX-2 activity in colon carcinoma cells to downregulate production of angiogenic factors, and inhibition of COX-1 activity in endothelial cells to suppress endothelial tube formation.[53]

Another study examined the role of COX-1 and COX-2 in tumor growth and angiogenesis using isografts of Lewis lung carcinoma (LLC) cells in COX-deficient "knockout" mice (*COX-1*$^{-/-}$ or *COX-2*$^{-/-}$) or coxib-treated (celecoxib or SC-58125) wild-type mice. Tumor growth was diminished both in size and speed in *COX-2* null mice compared with untreated wild-type mice. However, no such difference in tumor growth was observed between *COX-1* null mice and control mice. Furthermore, prior treatment with a coxib inhibited tumor growth, but to a lesser degree than tumor growth in *COX-2* null mice. Angiogenesis was also measured using this model, and results from these experiments suggested that COX-2 activity is essential for tumor angiogenesis, implying again that COX-2 activity promotes tumor growth.[57]

The chemopreventive effect of COX inhibition has been seen in various animal models of colon

cancer. The tumor load in *MIN* mice was decreased significantly and in a dose-dependent manner by the nonselective NSAID piroxicam.[58] These results were confirmed in a study of *MIN* mice treated with sulindac.[59]

Celecoxib demonstrated a chemopreventive effect in male rats in all phases of colon carcinogenesis: initiation, promotion, and progression. The incidence of azoxymethane-induced colon tumors was inhibited in celecoxib-treated rats by 93%; the multiplicity of colon tumors was inhibited by 97%, and the overall colon tumor burden was suppressed by more than 87%.[60]

Rofecoxib resulted in a similar dose-dependent reduction in the number and size of intestinal and colon polyps in *MIN* ($Apc^{\Delta 716}$) mice. Using a rofecoxib dose comparable in plasma concentration to that achieved in humans treated with rofecoxib 25 mg once daily, there was a 55% reduction in the number of all intestinal polyps and an 80% reduction in the number of polyps more than 1 mm in size.[49]

Based on these preclinical findings, large epidemiological studies were conducted to examine the impact of NSAID use on the development of colon cancer. Almost every study found a strong correlation between continuous NSAID use and decreased incidence of CRC in humans.[47]

The mounting evidence from preclinical and epidemiological studies was the basis for clinical trials of NSAID treatment for individuals with FAP. Results from three controlled clinical trials found that treatment with sulindac resulted in substantial regression of adenomatous polyps.[61–63] However, virtually all patients experienced regrowth of adenomatous polyps after sulindac therapy was discontinued.[7,54,64]

In a recent clinical trial, celecoxib 400 mg twice daily for 6 months in 30 patients with FAP resulted in a 28% reduction in the mean number of colorectal polyps ($P = .003$) and a 30.7% reduction in polyp size ($P = .001$).[48] Based on these findings, celecoxib received US Food and Drug Administration approval for the treatment of FAP.

Implication of COX-2 in the promotion of colon cancer

There is substantial evidence that the COX-2 isozyme plays a crucial role in the promotion of FAP and CRC.

- Significant upregulation of COX-2 but not COX-1 occurs in animal models and human samples of FAP polyps and colorectal tumors.[50–52]
- COX-2–generated prostaglandins produce angiogenic factors and promote tumor angiogenesis.[53]
- PGE_2, produced by COX-2 in colon tumors, suppresses apoptosis in human CRC cell lines and colon tumors.[55]
- Both celecoxib and rofecoxib have a COX-2–specific chemopreventive effect in animal models of CRC when compared with nonselective NSAIDs.[49,60]
- Celecoxib is approved as an adjunct to standard care for the treatment of FAP, a premalignant condition that leads to colon cancer if not treated.

■ CANCER PAIN

Cancer, the second leading cause of death in the United States, is often associated with uncontrolled pain.[8] In 1986, the World Health Organization (WHO) developed a three-step therapeutic guideline, called the WHO analgesic ladder, to improve the management of increasing levels of cancer pain.[65] NSAID therapy is recommended by the WHO for use at all three steps on the analgesic ladder, either alone or in combination with an opioid and adjuvant analgesic (other drugs that enhance analgesic effects).[8,66–68]

Inflammation and cancer pain

Cancer pain is often triggered by the release of inflammatory cytokines from active tumors.[8] NSAIDs produce analgesia in part by inhibiting the release of these inflammatory mediators, thus reducing nocioceptive transmission.[8,66,69]

The most common cause of cancer pain is tumor infiltration of bone.[8,68] Bone metastases occur as a consequence of breast cancer, prostate cancer, lung cancer, or multiple myeloma.[8] One likely mechanism of pain secondary to bone metastasis is the secretion of prostaglandins by carcinomas.[8,68] For this reason, NSAIDs should be included in any regimen to control pain associated with bone metastasis.[8,68–70]

Opioid-sparing benefit of NSAIDs

Because NSAIDs do not activate opioid receptors, they can provide additive pain relief when combined with an opioid analgesic.[8,68] Thus, combining an NSAID with an opioid analgesic may provide adequate pain control with a clinically significant reduction in opioid dosage.[69] This opioid-sparing effect of NSAID therapy allows the clinician to diminish the side effects associated with opioid

therapy without sacrificing pain control.[68,70]

However, nonselective NSAIDs have clinically significant adverse effects that differ from those of opioids, which have dose-dependent side effects. It is not always possible to predict which patients are at increased risk of developing an NSAID-induced side effect.[69] Furthermore, catastrophic or irreversible idiosyncratic side effects, which are not always preceded by a minor side effect, may occur without any warning.[8,69]

Clinical factors that increase the risk of an unacceptable adverse effect with traditional NSAID therapy are often present in patients with cancer, limiting the clinical utility of these agents.[65,69] For example, the risk of developing NSAID-associated agranulocytosis is greater in cancer patients who are often pancytopenic as a consequence of their cancer treatments. Similarly, aspirin-associated platelet dysfunction via acetylation of surface proteins is more likely to be clinically significant in cancer patients who are often thrombocytopenic due to chemotherapy or radiation therapy.[66,68,69] In these patients, nonacetylated salicylates (eg, salsalate, choline magnesium trisalicylate) or even acetaminophen are routinely used as alternatives to traditional NSAIDs.[66,68] The potential for toxicity is increased when both salicylates and nonselective NSAIDs are combined with methotrexate therapy.

NSAID-associated GI side effects such as dyspepsia are also more likely to occur in cancer patients, who often experience GI toxicities following chemotherapy.[68] The possibility of developing NSAID-associated GI ulceration, perforation, or frank bleeding is more likely to develop in cancer patients who often are thrombocytopenic, or to become clinically significant in patients who are chronically anemic as a consequence of their treatment.[68,69]

Coxibs: another option for cancer pain management

Oncologists are replacing nonselective NSAIDs, nonacetylated salicylates, and acetaminophen with coxib therapy, chosen for its safety profile. Surgical oncologists are exploring the use of coxibs both preoperatively, as preemptive analgesic therapy, and during the postoperative period to reduce opioid usage and speed the recovery process.

Guidelines for the use of NSAIDs, largely empiric, are drawn from extensive clinical experience.[70] Some anecdotal reports have found that celecoxib is less effective than traditional nonselective NSAIDs in managing cancer pain. Conversely, rofecoxib (25 mg/day or 50 mg/day) seems to be more effective than nonselective NSAIDs in managing cancer pain when combined with an opioid.

■ CONCLUSION

There are several patient groups other than high-risk arthritis patients that may benefit from coxib therapy. The data from epidemiological studies suggest that chronic use of NSAIDs may have a chemopreventive effect on the development of AD, and some clinical trials have shown a slowing of AD symptoms with NSAID treatment. A recent prospective study found that nonselective NSAIDs may be protective against AD.[71] The benefits of coxib treatment of AD are under study and will become known in the coming years.

Preclinical studies suggest that COX-2 inhibition should be a therapeutic target for the chemoprevention of CRC. One coxib is indicated for the treatment of the premalignant condition FAP. Depending on the outcome of current clinical trials, coxibs may be approved soon for adjunctive treatment and/or chemoprevention of CRC.

Palliative care clinicians and oncologists are increasingly using coxibs to manage cancer pain because of their opioid-sparing effect and their lack of the adverse effects typically associated with NSAID or opioid therapy.

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