August 15, 2001

VISN Formulary Leaders:

The Pharmacy Benefits Management/Medical Advisory Panel was asked to comment on the use of the cyclooxygenase 2 (COX-2) inhibitors, celecoxib or rofecoxib, for the chemoprevention of colorectal cancer or adenomas. Since available data are primarily from epidemiological research and from small intervention studies, there is insufficient evidence to advocate for or against using any nonsteroidal anti-inflammatory agent (NSAID), selective or nonselective, in the treatment of colorectal cancer. Nor is the evidence sufficient to identify appropriate candidates for this mode of therapy. Thus, our intention is to discuss the current state of evidence and to recommend an interim course of action when clinicians request a COX-2 inhibitor for treatment or prevention of colorectal cancer or adenoma.

For the year 2000, it was estimated that 130,000 people will develop colon cancer in the Unites States and nearly 45% of those will die from their disease. Colon cancer is reported to be the second-leading cause of death due to cancer in the US.[1] In epidemiologic studies, nonsteroidal anti-inflammatory drugs (NSAIDs), primarily aspirin, have been shown to reduce the relative risk of colorectal carcinoma by 40-50%.[2] Non-aspirin NSAIDs have also been found to reduce the incidence of colorectal cancer[3], similar to that seen in studies with aspirin, and colorectal adenoma.[4] Sulindac, at doses of 300 to 400 mg daily, was shown to significantly reduce the number of polyps in 3 small studies of patients with familial adenomatous polyposis (FAP).[5-7] More recently, the cyclooxygenase 2 (COX-2) selective agent, celecoxib, was also found to reduce the polyp burden in patients with FAP when taken at a dose of 400 mg twice daily.[8] Celecoxib is currently the only NSAID (COX-2 specific or nonselective) that is FDA approved for the treatment of FAP.

The development of an adenomatous polyp is felt to be an intermediary in the progression to colon cancer. Adenomatous polyps are found in about 1/3 of the population by age 50, and 50% of people by age 70 years.[2] Patients with FAP have almost a 100% chance of developing colon cancer, because of the large number of polyps occurring in these individuals, but account for only about 1% of the cases of colorectal carcinoma.[2]

Expression of cyclooxygenase-2, the inducible COX, has been shown to be 2-50 fold higher in colorectal adenocarcinomas compared to the normal surrounding intestinal tissue.[9,10] COX-2 is induced in the presence of inflammation, colorectal adenomas and colorectal cancer.[11,12] Therefore, the primary mechanism for chemoprevention against colorectal adenoma and carcinoma is thought to be related to inhibition of COX-2.

To date, there is no evidence to suggest that the available COX-2 inhibitors (celecoxib or rofecoxib) have any advantage over nonselective NSAIDs in terms of their effect on the development of colorectal carcinoma or adenoma. There are no clinical trials or analyses (published or enrolling patients) in which celecoxib or rofecoxib have been compared directly with a nonselective NSAID for the chemoprevention of colorectal cancer or adenoma. In addition, there are no published, long-term observations or investigations, showing a reduced relative risk for the development of colorectal carcinoma with the COX-2 agents as opposed to aspirin and NSAIDs where these epidemiologic data exist.

Nonselective NSAIDs, aspirin and the selective COX-2 inhibitors all inhibit COX-2. Therefore, since a primary target for chemoprevention is aimed at inhibition of COX-2 and since there are no data proving an efficacy advantage for the COX-2 agents, the decision to prescribe a COX-2 selective agent for chemoprevention should be based upon the current PBM/MAP criteria for the nonformulary use of COX-2 inhibitors.[13]

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