Chemoprevention of Colorectal Adenoma with Ursodeoxycholic Acid

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.

Study Overview

Objective. To determine the efficacy of ursodeoxycholic acid (UDCA) in preventing colorectal adenoma recurrence.

Design. Randomized, double-blind, placebo-controlled trial.

Setting and participants. Patients were recruited from a preexisting network of 80 gastroenterologists from the Phoenix and Tucson metropolitan areas. Patients were included if they were aged 40 to 80 years, had 1 or more colorectal adenomas with a diameter of 3 mm or more removed during colonoscopy examination within the prior 6 months, had no clinical evidence of organic disease, and had no invasive cancer within the previous 5 years.

Intervention. Patients were randomized to either UDCA ($n = 661$) 8 to 10 mg/kg per day or placebo ($n = 624$). The duration of treatment was 3 years or until completion of follow-up colonoscopy.

Main outcome measures. Recurrence of colorectal adenoma, defined as 1 or more colorectal adenomas 6 months or more after the baseline colonoscopy. Colorectal adenomas were considered advanced if they were 10 mm or more in diameter, tubulovillous or had villous histology, high-grade dysplasia, or adenocarcinoma.

Main results. 48 patients in the UDCA group and 45 patients in the control group did not undergo a follow-up colonoscopy and were excluded, resulting in 613 and 579 patients available for analysis, respectively. Baseline characteristics were similar in the 2 study groups. 43.9% of participants allocated to placebo experienced a recurrent adenoma compared with 41% in the UDCA group. The risk ratio for adenoma recurrence in the UDCA group compared with the placebo group was 0.93 (95% confidence interval [CI], 0.82–1.07). 19% of participants receiving placebo were found to have advanced adenomas on follow-up colonoscopy compared with 16.2% UDCA patients. The risk ratio for advanced adenoma in the UDCA group compared with the control group was 0.85 (95% CI, 0.66–1.09). The rate of recurrent adenomas that had high-grade dysplasia was 8.7% in the control group and 5.5% in the UDCA group (adjusted odds ratio, 0.61 [95% CI, 0.39–0.96]). Rates of adverse events between the 2 study arms were similar except for diarrhea, with 6.41% of control patients experiencing diarrhea compared with 10.4% of UDCA participants ($P = 0.01$).

Conclusion. UDCA may be effective at reducing colorectal adenoma recurrence in individuals with high-grade dysplasia. Overall, UDCA appeared well tolerated but was associated with a significant increase in diarrhea.

Commentary

With over 56,000 anticipated colorectal cancer deaths for 2005, colorectal cancer is a substantial cause of morbidity and mortality in the United States [1]. Colorectal cancer is one of the best-studied malignancies, and many of the mechanisms underlying colorectal cancer formation have been elucidated. The most well-accepted model of colorectal tumorigenesis suggests that colorectal cancers almost exclusively develop from colorectal polyps that transition through a series of steps that can take decades [2]. This insight provides the rationale for colonic adenoma identification and removal as a means to prevent colorectal cancer, and randomized trials have demonstrated the effectiveness of this strategy [3]. Another potential strategy for reducing colorectal cancers is through chemoprevention. Because secondary bile acids such as deoxycholic acid (DCA) appear to alter intracellular signaling and gene expression and to enhance cell proliferation within colonic epithelium [4], agents that oppose the action of DCA could prove to be effective chemopreventive agents.

UDCA is a tertiary bile acid that appears to inhibit cell proliferation and antagonize some of the carcinogenic effects of DCA. Earlier clinical trials have suggested that these agents might reduce colorectal adenomas in patients with primary biliary cirrhosis and primary sclerosing cholangitis [5,6]. To determine the effectiveness of UDCA in otherwise healthy individuals, Alberts et al conducted a large, randomized, double-blind, placebo-controlled trial. Although the rates of recurrent adenomas were reduced in the intervention group, the difference did not meet statistical significance and thus

could be a chance finding. On secondary analysis, UDCA did appear to reduce the risk of recurrent high-grade dysplasia; this is an important finding, as high-grade dysplasia is typically the final step before malignant transformation.

Several reasons could explain why the investigators' findings were not significant. First, colorectal cancer can take several decades to progress from normal colonic epithelium to frank malignancy, and as a result, the study duration may have been too brief. Second, the study was only powered to detect a 20% reduction in colorectal cancer recurrence, which may have been an overly optimistic estimate of the intervention's overall effectiveness.

Applications for Clinical Practice

Although UDCA treatment did not reach statistical significance, it appears promising as chemoprevention for colorectal adenoma recurrence. Because of the associated increase in UDCA-related diarrhea, clinicians should probably refrain from using UDCA for their patients with colorectal adenoma until further clinical trials have been conducted.

–Review by Harvey J. Murff, MD, MPH

References

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