THE EFFECT OF CELECOXIB, A CYCLOOXYGENASE-2 INHIBITOR, IN FAMILIAL ADENOMATOUS POLYPOSIS

GIDEON STEINBACH, M.D., PH.D., PATRICK M. LYNCH, M.D., J.D., ROBIN K.S. PHILLIPS, M.B., B.S., MARINA H. WALLACE, M.B., B.S., ERNEST HAWK, M.D., M.P.H., GARY B. GORDON, M.D., PH.D., NAOKI WAKABAYASHI, M.D., PH.D., BRIAN SAUNDERS, M.D., YU SHEN, PH.D., TAKASHI FUJIMURA, M.D., LI-KUO SU, PH.D., AND BERNARD LEVIN, M.D.

ABSTRACT

Background Patients with familial adenomatous polyposis have a nearly 100 percent risk of colorectal cancer. In this disease, the chemopreventive effects of nonsteroidal antiinflammatory drugs may be related to their inhibition of cyclooxygenase-2.

Methods We studied the effect of celecoxib, a selective cyclooxygenase-2 inhibitor, on colorectal polyps in patients with familial adenomatous polyposis. In a double-blind, placebo-controlled study, we randomly assigned 77 patients to treatment with celecoxib (100 or 400 mg twice daily) or placebo for six months. Patients underwent endoscopy at the beginning and end of the study. We determined the number and size of polyps from photographs and videotapes; the response to treatment was expressed as the mean percent change from base line.

Results At base line, the mean (±SD) number of polyps in focal areas where polyps were counted was 15.5±13.4 in the 15 patients assigned to placebo, 11.5±8.5 in the 32 patients assigned to 100 mg of celecoxib twice a day, and 12.3±8.2 in the 30 patients assigned to 400 mg of celecoxib twice a day (P=0.66 for the comparison among groups). After six months, the patients receiving 400 mg of celecoxib twice a day had a 28.0 percent reduction in the mean number of colorectal polyps (P=0.003 for the comparison with placebo) and a 30.7 percent reduction in the polyp burden (the sum of polyp diameters) (P=0.001), as compared with reductions of 4.5 and 4.9 percent, respectively, in the placebo group. The improvement in the extent of colorectal polyposis in the group receiving 400 mg twice a day was confirmed by a panel of endoscopists who reviewed the videotapes. The reductions in the group receiving 100 mg of celecoxib twice a day were 11.9 percent (P=0.33 for the comparison with placebo) and 14.6 percent (P=0.09), respectively. The incidence of adverse events was similar among the groups.

Conclusions In patients with familial adenomatous polyposis, six months of twice-daily treatment with 400 mg of celecoxib, a cyclooxygenase-2 inhibitor, leads to a significant reduction in the number of colorectal polyps. (N Engl J Med 2000;342:1946-52.)

HUMAN colon cancer develops in a stepwise fashion from normal mucosa to adenomatous polyps to carcinoma. Mutation in the adenomatous polyposis coli (*APC*) gene commonly occurs early in the development of sporadic adenomas.[1] Patients with familial adenomatous polyposis have an inherited germ-line *APC* mutation[2] that results in hundreds of adenomatous polyps and a nearly 100 percent risk of colon cancer. Management includes prophylactic proctocolectomy, or colectomy followed by sigmoidoscopic surveillance and rectal polypectomy. Because the adenoma-to-carcinoma sequence in familial adenomatous polyposis resembles sporadic colon carcinogenesis,[1] studies of familial adenomatous polyposis may contribute to the prevention of sporadic adenomas and colon cancer.

Nonsteroidal antiinflammatory drugs (NSAIDs) reduce the incidence of carcinogen-induced colon tumors in rodents.[3,4] NSAIDs are associated with a reduced incidence of and mortality from sporadic adenoma and colon cancer in epidemiologic studies.[5-8] In early clinical studies[9,10] and small, randomized, placebo-controlled trials,[11-13] sulindac caused the regression of colorectal adenomas in patients with familial adenomatous polyposis. However, the gastrointestinal toxicity associated with conventional NSAIDs may limit their long-term use for cancer prevention.[14]

NSAIDs are inhibitors of the cyclooxygenase enzyme family, which catalyzes the metabolism of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes. The cyclooxygenase-1 isoform is constitutively expressed in most tissues, where it medi-

From the University of Texas M.D. Anderson Cancer Center, Houston (G.S., P.M.L., N.W., Y.S., T.F., L.-K.S., B.L.); the Imperial Cancer Research Fund, St. Mark's Hospital, London (R.K.S.P., M.H.W., B.S.); the National Cancer Institute, Bethesda, Md. (E.H.); and G.D. Searle, Skokie, Ill. (G.B.G.). Address reprint requests to Dr. Steinbach at the University of Texas M.D. Anderson Cancer Center, Division of Cancer Prevention, Box 203, 1515 Holcombe Blvd., Houston, TX 77030, or at gsteinb@aol.com.

Other authors were Louis Godio, Ph.D. (G.D. Searle, Skokie, Ill.), Sherri Patterson, B.A. (M.D. Anderson Cancer Center, Houston), Miguel A. Rodriguez-Bigas, M.D. (Roswell Park Cancer Institute, Buffalo, N.Y.), Susan L. Jester, M.S. (G.D. Searle), Karen L. King, M.S. (G.D. Searle), Maria Schumacher, M.B.A. (National Cancer Institute, Bethesda, Md.), James Abbruzzese, M.D. (M.D. Anderson Cancer Center), Raymond N. DuBois, M.D., Ph.D. (Vanderbilt University Medical Center, Nashville), Walter N. Hittelman, Ph.D. (M.D. Anderson Cancer Center), Stuart Zimmerman, Ph.D. (M.D. Anderson Cancer Center), Jeffrey W. Sherman, M.D. (G.D. Searle), and Gary Kelloff, M.D. (National Cancer Institute).

ates physiologic functions such as gastric mucosal cytoprotection and regulation of platelet aggregation. Its inhibition may account for many of the common side effects of NSAIDs, including gastric ulceration and gastrointestinal hemorrhage.[14,15] The cyclooxygenase-2 isoform is induced in response to cytokines and growth factors and is expressed in inflammatory disease, premalignant lesions (such as colorectal adenomas), and colon cancer.[16-18] Its inhibition has not been associated with gastric ulceration.[15,19-21] However, the long-term effects of selective cyclooxygenase-2 inhibitors as compared with those of traditional NSAIDs remain to be determined.[22] Experimental evidence supports the concept that the chemopreventive effects of NSAIDs may be due at least in part to inhibition of cyclooxygenase-2.[23,24] Hence, selective inhibition of cyclooxygenase-2 offers a potential pharmacologic strategy for the prevention of colorectal adenomas.

To determine whether inhibition of cyclooxygenase-2 could reduce the extent of polyposis in patients with familial adenomatous polyposis, we studied the effect of celecoxib, an agent that selectively inhibits cyclooxygenase-2.[21]

METHODS

Patients

Patients with familial adenomatous polyposis who were 18 to 65 years of age, who had not had their entire colorectum removed, and who had five or more polyps 2 mm or more in diameter that could be assessed endoscopically, were eligible. Exclusion criteria included a history of colectomy within the previous 12 months or colectomy anticipated within 8 months after randomization; use of NSAIDs or aspirin three or more times a week within 6 months of randomization or one or two times a week within 3 months of randomization; or abnormal results of serum laboratory tests (complete blood count and liver-function and renal-function tests).

The study was approved by the institutional review board of the University of Texas M.D. Anderson Cancer Center and the ethics committee of St. Mark's Hospital, London. Written informed consent was obtained from all patients.

Study Design

The study was randomized, double-blinded, and placebo-controlled. It was conducted between December 1996 and December 1998 at the M.D. Anderson Cancer Center in Houston and St. Mark's Hospital in London. One hundred eight patients who were eligible for screening underwent endoscopy; 29 had insufficient polyps for inclusion in the study, and 2 required colectomy for advanced disease (a rectal cancer and a large sessile adenoma). According to the protocol, 75 patients were initially randomly assigned in a 2:2:1 ratio to receive celecoxib (Celebrex, G.D. Searle, Skokie, Ill.), either 100 mg twice daily or 400 mg twice daily, or an identical-appearing placebo orally for six months. The placebo contained 250 mg of lactose. Two additional patients were assigned to the group receiving 100 mg of celecoxib twice daily after two patients were withdrawn because of noncompliance. The study drug and matching placebo were provided by G.D. Searle.

The six-month duration of the study and the end point of adenoma regression were based on previous trials of sulindac that demonstrated an effect on polyp regression within six months of treatment.[9-13] A clinical trial aimed at the prevention of carcinoma, on the other hand, would require many years of study and therefore was not considered feasible for the initial testing of the efficacy of a drug. Evaluations at base line and month 6 included a history taking, physical examination, and endoscopy, with biopsies of the intact or residual colorectum, stomach, and duodenum. Testing for *APC* gene mutations was performed at base line.[25]

Compliance was monitored by means of pill counts and review of diaries completed by the patients. Safety was monitored with a comprehensive symptom questionnaire administered by telephone at two-to-four-week intervals that elicited information on adverse events and by clinical laboratory evaluations at base line and at one, three, and six months. Adverse events were graded in accordance with the National Cancer Institute Common Toxicity Criteria.[26]

Endoscopy

At the base-line endoscopy, an India-ink tattoo was placed in the rectum, colon, or both near a small area with a high density of polyps. The base-line and six-month endoscopic examinations were videotaped, and a series of photographs was taken with the tattoo, appendix, or ileocecal valve positioned centrally and peripherally. These photographs were used for quantitative measurements of the number and size of polyps. Polyps for biopsy were taken from areas that were not photographed for scoring.

Enumeration and Measurement of Polyps

To ascertain that the same area was scored at base line and at month 6, polyps were counted in pairs of photographs. One investigator, other than the endoscopist, who did not know the treatment, performed the scoring. Videotapes were used to resolve ambiguities and confirm polyp counts. The diameter of a polyp was measured with the aid of a standardized endoscopic ruler or biopsy forceps included in the photographic field to serve as a scale. Because in patients with familial adenomatous polyposis the colon is studded with microscopic and poorly visible lesions, only distinct polyps at least 2 mm in diameter were counted.

A qualitative assessment of the total extent of colorectal polyposis was conducted by each of five endoscopists experienced in the management of familial adenomatous polyposis (two from each of the study centers and one from a nonparticipating polyposis center) during joint videotape-review sessions. The first of each pair of videos (obtained at base line and month 6) was scored as the same as, better than, or worse than the second, without the endoscopists' being aware of the temporal sequence or treatment group. A score of "better" or "worse" indicated that there was a clear difference in the total extent of polyp involvement. To avoid bias, videotapes of three colorectal regions (cecum and ascending colon; transverse, descending, and sigmoid colon; and rectum) were assessed separately without the endoscopists' being aware of whether the segments came from the same patient.

Statistical Analysis

All 77 randomly assigned patients were included in the intention-to-treat analysis of toxicity and polyp number, size, and burden. Analysis of the endoscopic videotape assessments was performed in the patients for whom the requisite videotapes were available.

The quantitative response variables were the percent change from base line in polyp number and polyp burden, defined as the sum of the polyp diameters. The percent change in each patient was calculated on the basis of the photographs at the tattoo, appendix, and ileocecal valve, and the mean change was then calculated for each study group. Efficacy was evaluated by comparing the mean percent change from base line in each treatment group with that in the placebo group by the Wilcoxon rank-sum test.

Whether treatment affected the polyp count at six months was also analyzed in a multivariate linear regression model with adjustment for base-line covariates. Two variables indicating the treatment (100 or 400 mg twice a day) were included in the model, and the other base-line covariates were the number of polyps, sex, age, study site, and surgical status (whether the patient had previously

undergone colectomy). We employed a logarithmic transformation of both the base-line and the final polyp-count values to eliminate the skewness in that distribution.

In the qualitative assessment of response, based on review of the endoscopic videotapes, each segment was assigned a score of 1 for better, 0 for same, or −1 for worse, and the mean of the five physicians' scores for each treatment group was compared with that for the placebo group with use of the Wilcoxon rank-sum test. The response of each videotaped colorectal segment (cecum and ascending colon; transverse, descending, and sigmoid colon; and rectum) was analyzed separately. In addition, the response of the total colorectum, defined for each patient as the mean score for all colorectal segments assessed, was analyzed.

Adverse events, including those with an onset within 30 days after the end of treatment, were coded according to World Health Organization Adverse Reaction Terminology and graded for severity with the National Cancer Institute Common Toxicity Criteria.[26] Clinical laboratory data were compared between treatment groups by one-way analysis of variance applied to the change from base line to month 1, month 3, month 6, or early termination.

The Kruskal–Wallis test was used to compare base-line continuous variables among the three treatment groups, and the chi-square test or Fisher's exact test was used to examine associations between nominal variables. All tests were two-sided, and a P value of less than 0.05 was considered to indicate statistical significance.[27] No interim analyses were performed.

RESULTS

Patients

Seventy-seven patients were enrolled: 36 at the M.D. Anderson Cancer Center and 41 at St. Mark's Hospital. The treatment groups were similar with regard to race or ethnic group, sex ratio, surgical status, and number of polyps, but they differed in age: the group assigned to 400 mg of celecoxib twice a day was younger (33.1 years) than the group assigned to 100 mg of celecoxib twice a day (38.6 years) and the placebo group (39.9 years) (Table 1). Sixty-six patients had an identified *APC* mutation, and two additional patients had relatives with known *APC* mutations. Seventy-two of the 77 patients completed the treatment. More than 90 percent of the patients who completed the study took at least 80 percent of the study drug. At base line, the placebo group had a mean (±SD) of 15.5±13.4 polyps, the group assigned to 100 mg of celecoxib twice a day had a mean of 11.5±8.5 polyps, and the group assigned to 400 mg of celecoxib twice a day had a mean of 12.3±8.2 polyps in the focal areas where polyps were counted (P=0.66 for the comparison among groups).

Table 1. Base-Line Characteristics of the Patients with Familial Adenomatous Polyposis.*

Characteristic	Placebo (N=15)	100 mg of Celecoxib Twice Daily (N=32)	400 mg of Celecoxib Twice Daily (N=30)	P Value
Age — yr	39.9±11.3	38.6±10.0	33.1±10.9	0.04†
Sex — no. (%)				0.84‡
Male	9 (60)	17 (53)	18 (60)	
Female	6 (40)	15 (47)	12 (40)	
Race or ethnic group — no. (%)				0.87§
Black	0	1 (3)	1 (3)	
White	15 (100)	29 (91)	26 (87)	
Hispanic	0	2 (6)	3 (10)	
Height — cm	171.5±7.7	169.9±9.7	169.1±11.6	0.74†
Weight — kg	74.6±16.4	74.4±12.7	71.1±15.4	0.39†
Surgical status — no. (%)				0.45‡
Intact colon	5 (33)	8 (25)	12 (40)	
Colectomy	10 (67)	24 (75)	18 (60)	
No. of polyps	15.5±13.4	11.5±8.5	12.3±8.2	0.66†
Polyp size — mm	2.9±0.5	2.9±0.7	2.9±0.6	0.63†
Polyp burden — mm¶	44.7±36.5	34.8±28.1	37.6±29.4	0.65†

*Plus–minus values are means ±SD.
†The P value was calculated by the Kruskal–Wallis test.
‡The P value was calculated by the chi square test.
§The P value was calculated by Fisher's exact test.
¶The polyp burden was calculated as the sum of the polyp diameters.

Response to Treatment

Treatment with 400 mg of celecoxib twice daily for six months was associated with a significant reduction from base line in the number of colorectal polyps as compared with the placebo group (28.0 percent vs. 4.5 percent, P=0.003) (Table 2 and Fig. 1). The group receiving 100 mg of celecoxib twice daily had a reduction of 11.9 percent as compared with 4.5 percent in the placebo group (P=0.33). Multivariate linear regression analysis confirmed that 400 mg of celecoxib twice daily reduced the number of colorectal polyps (P=0.005) after adjustment for age, sex, surgical status (colectomy vs. intact colon), number of polyps at base line, and investigational institution.

A reduction of 25 percent or more in the mean number of colorectal polyps was seen in 53 percent of the patients in the group receiving 400 mg of celecoxib twice daily (P=0.003 for the comparison with placebo), 31 percent of the patients in the group receiving 100 mg of celecoxib twice daily (P=0.08), and 7 percent of patients in the placebo group. Intention-to-treat analysis of the specific response of rectal polyps as distinct from colonic polyps showed a mean reduction in the number of rectal polyps of 22.5 percent (P=0.01 for the comparison with the placebo group) in the group receiving 400 mg of celecoxib twice daily and of 3.4 percent (P=0.52 for the comparison with the placebo group) in the group receiving 100 mg of celecoxib twice daily, as compared with a mean increase of 3.1 percent in the placebo group (Table 2).

Whereas the number of polyps was quantified in designated small areas adjacent to a tattoo or anatomical landmark, the full extent of colorectal polyposis was assessed qualitatively from videotapes of complete anatomical segments of the colorectum by a panel of five endoscopists. The videotapes showed that in the group receiving 400 mg of celecoxib twice daily, sig-