

A Randomized, Double-Blind, Placebo-Controlled Trial of the Effects of Rofecoxib, a Selective Cyclooxygenase-2 Inhibitor, on Rectal Polyps in Familial Adenomatous Polyposis Patients

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ABSTRACT

Purpose: The aim of this study was to examine the effect of a specific cyclooxygenase-2 inhibitor, rofecoxib, on rectal polyps in familial adenomatous polyposis patients.

Experimental Design: This was a randomized, double-blind, placebo-controlled study of the efficacy and safety of rofecoxib in the rectum. Initially, 21 patients were assigned randomly in a 1:1 ratio to receive either 25 mg rofecoxib once a day or a placebo p.o. for 9 months. Patients underwent endoscopy at the beginning of the study and then every 3 months thereafter. We reviewed the videotapes to measure the number and size of polyps in the same area throughout the study period in each individual patient.

Results: The polyp number, measured as the percentage of change from the baseline values, was significantly decreased in the rofecoxib group at 3, 6, and 9 months. At 9 months, the polyp number in the rofecoxib group decreased by 6.8% from the baseline values, whereas that in the placebo group increased by 3.1%. The 9.9% difference between the rofecoxib and placebo groups was statistically significant ($P = 0.004$). At 9 months, the rofecoxib group showed a significant reduction from the baseline in polyp size as compared with the placebo group ($-16.2%$ versus $1.5%$; $P < 0.001$). There was no statistically significant increase in the incidence of any adverse events in treatment with rofecoxib compared with placebo ($P = 0.922$).

Conclusions: In this study, once-daily treatment with 25 mg rofecoxib, a cyclooxygenase 2-specific inhibitor, signifi-

cantly decreased the number and size of rectal polyps in familial adenomatous polyposis patients.

INTRODUCTION

FAP² is an autosomal dominant disease caused by a germline mutation in the *APC* gene located at chromosome 5q21 (1–3). Patients with FAP develop hundreds to thousands of adenomatous polyps, and they are at a nearly 100% risk of colorectal cancer (4). Management includes prophylactic proctocolectomy or colectomy followed by sigmoidoscopic surveillance and rectal polypectomy. Studies of FAP may contribute to the prevention of colorectal cancer in patients with not only in FAP but also sporadic polyps.

Epidemiological studies have shown that regular use of aspirin-like drugs or NSAIDs reduces the incidence of and mortality from sporadic adenoma and colorectal cancer (5–7). Recent studies in two large randomized, double-blind clinical trials have demonstrated that aspirin reduces the risk of recurrent adenomas among patients with a history of colorectal cancer or adenomas (8, 9). There are case reports indicating that adenomatous polyps may regress in FAP patients who receive sulindac, an NSAID (10, 11). In small, randomized, placebo-controlled trials, sulindac treatment produced a significant regression of colorectal adenomas in patients with FAP (12–14). However, long-term use of conventional NSAIDs for cancer prevention is hampered by their strong gastrointestinal toxicity (15). In FAP, the chemopreventive effects of NSAIDs appear to be through their inhibition of COX-2 (16, 17). A COX-2-selective inhibitor, celecoxib, has been shown to decrease polyp number and size in chemically induced *Apc* mutant Min mouse (18). In a clinical trial with FAP patients, celecoxib has also been reported to have moderate efficacy in reduction of colonic polyps, at twice the maximum recommended dose for patients with osteoarthritis and rheumatoid arthritis (19). Rofecoxib is a COX-2-specific inhibitor, which has higher selectivity to COX-2 than celecoxib (20). *In vivo*, rofecoxib has been shown to reduce polyp number and size in the *Apc* mutant mouse; hence, rofecoxib is a potential chemopreventive agent in adenoma and colon cancer (21). The aim of this study was to examine the effect of rofecoxib at a clinically approved dose in the United States and Europe on rectal polyps in FAP patients.

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² The abbreviations used are: FAP, familial adenomatous polyposis; APC, adenomatous polyposis coli; NSAID, nonsteroidal anti-inflammatory drug; COX, cyclooxygenase.

Table 1 Schedule of the study

Months	Baseline	Treatment period									Post-treatment period			
		1	2	3	4	5	6	7	8	9	10	11	12	Discontinuation
Colonoscopy	X			X			X			X			X	X
Gastroduodenoscopy	X									X			X	X
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood pressure, body weight	X	X	X	X	X		X			X	X			X
Laboratory tests	X	X	X	X	X		X			X	X			X

MATERIALS AND METHODS

Patients. This was a randomized, double-blind, placebo-controlled study of the efficacy and safety of rofecoxib in reducing percentage area of disease in the rectum, and in reducing the extent of rectal polyposis. Twenty-one patients with FAP were enrolled in the study (11 males and 10 females, median age 30 years), recruited during their routine clinical follow-up at Kyoundo Hospital Sasaki Institute, (Tokyo, Japan) and Tokyo Medical and Dental University. Patients diagnosed as FAP on the basis of having at least 10 colorectal polyps at endoscopy and/or in colectomy specimens were eligible if they had five or more rectal polyps of ≥ 2 mm in diameter when assessed endoscopically, and if the rectal region was still intact. Accordingly, patients with attenuated FAP were not included. The age distribution of enrolled patients was 19–55 years. No patients were tested for APC mutations. Subjects included 13 postcolectomy patients. Although average time postcolectomy was 87 months, we did not exclude patients within 2 years after operations.

The following were the reasons for exclusion from the study: patients required colectomy for dense adenomas, had >10 -mm adenoma or malignant disease, use of an NSAID or aspirin within 1 month preceding the study, history of peptic ulcers or gastrointestinal hemorrhage, history of severe side-effects by NSAIDs, clinically significant abnormal results in laboratory data, history of active bacterial infection, drug hypersensitivity, absence of the use of effective birth control in women of childbearing age, or pregnancy.

The study was approved by the Institutional Review Boards of the investigative sites, and written informed consent was obtained from all of the patients. Because rofecoxib is not yet approved for clinical use in Japan, the protocol was submitted to and approved by Japanese Ministry of Health and Welfare. According to the protocol, 21 patients were initially assigned randomly in a 1:1 ratio to receive p.o. either 25 mg rofecoxib (Merck and Co., Inc.) or an identical-appearing placebo once daily for 9 months. The rofecoxib dose of 25 mg was selected on the basis of the standard therapy for osteoarthritis. The study was double-blind: treatment assignments were not revealed to any patients, investigators, or endoscopists until the drug treatment was completed and clinical data were collected. Patients ambulated to the study center monthly to be assessed for the compliance and safety. Adverse effects were also monitored monthly on their visits. Laboratory tests were performed before the start of the study (at the baseline), and after 1, 2, 3, 4, 6, 9, and 10 months during the study. The study schedule is shown in Table 1. Before the blind code was opened, 5 patients

were excluded from the efficacy analysis, although they were included in the safety analysis. Namely, 21 patients were included in the safety analysis, and 16 patients were included in the efficacy analysis. The following are reasons for 5 patients excluded from the efficacy analysis. One patient had no available endoscopic data before (at the baseline) the treatment, 1 had a history of total gastrectomy (difficult to evaluate the efficacy because of potential effects on drug absorption), 1 had used another NSAID for a treatment of an adverse effect, 1 discontinued within a month because of an adverse effect (gastroenteritis), and another requested to discontinue the drug treatment because of adverse effect (redness of legs and gingival pain).

Endoscopy. Videotaped colonoscopy with Olympus flexible colonoscopes was performed before the beginning of the study therapy (the baseline), every 3 months during the treatment, and at 3 months after the treatment. An intestinal enema was given as a pretreatment with 200–500 ml saline solution. The indigocarmine spraying method was used during the endoscopy so that no small or flat adenomas were overlooked. At the baseline endoscopy, the largest rectal polyp was identified as a landmark, and the diameters of this polyp as well as four more vicinal polyps were determined using the endoscopic ruler. The endoscopic examinations were videotaped, and a series of photographs were taken of the area near the landmark polyp. These photographs were used for quantitative measurements of the number and size of polyps. Follow-up gastroduodenoscopic examinations were performed at the baseline, 9 months, and 12 months, respectively.

Clinical Assessment. For each patient, the same investigator who performed the endoscopy reviewed the videotapes and prepared the video-photographs of polyps of the same area for evaluation throughout the study period. Independent endoscopists assessed the number and size of polyps based on these video-photographs. The efficacy of the treatment was assessed by separate investigators from those who performed the endoscopy or prepared the video-photographs.

Statistical Analysis. The number and average size of polyps were compared between the treatment groups using a covariance analysis model with factors for treatment and baseline as a covariate. The data were log-transformed for the analysis using the log values at month 9/at baseline, and the results were back-transformed to percentage changes from the baseline scale. For data from missing patients, their last observed values before the missing time point were carried forward for the purpose of plotting the mean values.

Table 2 Baseline characteristics of the patients with familial adenomatous polyposis^a

Characteristic		Placebo <i>n</i> = 9	Rofecoxib <i>n</i> = 12
Age	yr.	33.6 ± 14.8	32.3 ± 11.2
Gender	no. (%)		
Male		4 (44.4)	7 (58.3)
Female		5 (55.6)	5 (41.7)
Height	cm	161.2 ± 7.2	162.7 ± 4.5
Weight	kg	57.7 ± 12.9	51.8 ± 7.4
Surgical status	no. (%)		
Intact colon		3 (33.3)	5 (41.7)
Colectomy		6 (66.7)	7 (58.3)
No. of polyps		7.2 ± 3.3	8.0 ± 4.5
Polyp size	mm	3.3 ± 0.8	3.0 ± 0.7

^a Plus-minus values are means ± SD.

RESULTS

Demographic Characteristics. Twenty-one patients were enrolled: 14 at Kyoundo Hospital and 7 at Tokyo Medical and Dental University. There were no significant clinical differences in patient demographic characteristics between the treatment groups (Table 2).

Response to Treatment. The number of polyps, measured as the percentage of change from the baseline values, was significantly decreased in the group given rofecoxib at 3, 6, and 9 months (Fig. 1). At 9 months, the polyp number in the group given rofecoxib decreased by 6.8% from the baseline values, whereas in the group of placebo, it increased by 3.1%. The 9.9% difference between the rofecoxib and placebo groups was statistically significant ($P = 0.004$). Similar decreases were found in the polyp size (Fig. 2). At 9 months, the group given rofecoxib was associated with a significant reduction from the baseline in the size of rectal polyps as compared with the placebo group (-16.2% versus 1.5% ; $P < 0.001$). At 3 months after completion of rofecoxib treatment, the slight relapse of rectal polyps was seen. No patient showed complete disappearance of the polyps. Nine patients (5 in rofecoxib group and 4 in placebo group) had duodenal polyps at the baseline. There were no obvious changes found in any of the patients before breaking the code; therefore, we decided not to analyze the duodenal polyps.

Safety. Rofecoxib was well tolerated. The most common adverse effects were stomatitis and abdominal pain. One patient (8.3%) of 12 in the rofecoxib group reported a serious adverse effect, but none of 9 patients in the placebo group did. Namely, a patient in the rofecoxib group had gastroenteritis with several clinical symptoms (watery diarrhea, right lower quadrant pain, and general fatigue). The study drug was discontinued, and gastroenteritis disappeared. There was no statistically significant difference in the incidence of any adverse effects between the two groups ($P = 0.922$). No ulceration was observed in any patients on the follow-up gastroduodenoscopy. No peripheral edema was found in any patients. Likewise, there were no significant changes in blood pressure in the patients of either group. There were also no clinically significant changes in the laboratory test results such as complete blood count, serum proteins, transaminases, alkaline phosphate, lactate dehydrogenase, blood urea nitrogen, creatinine, uric acid, electrolytes or iron, or in urinalysis data.

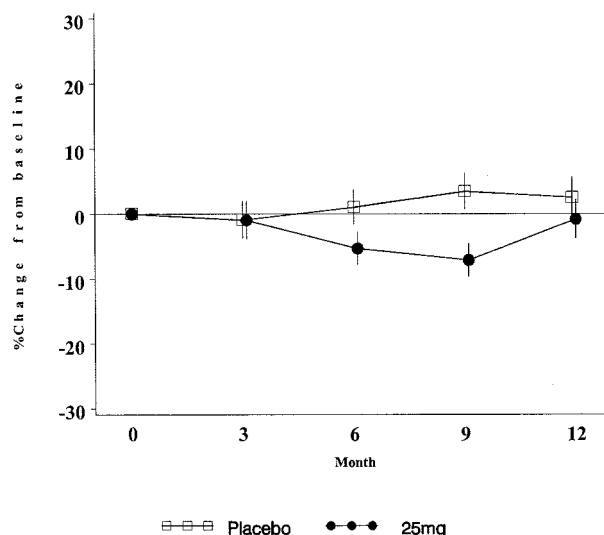


Fig. 1 Mean percentage of change from base line in the number of polyps; bars, \pm SE. At 9 months, the polyp number in the group given rofecoxib decreased by 6.8% from the baseline values, whereas in the group of placebo, it increased by 3.1%. The 9.9% difference between the rofecoxib and placebo groups was statistically significant ($P = 0.004$).

DISCUSSION

In this randomized, double-blind, placebo-controlled study, we have demonstrated that rofecoxib at 25 mg is effective in reducing the number and size of rectal polyps in FAP patients. Accumulating evidence indicates that COX-2 plays an important role in colorectal tumorigenesis. The present clinical findings are consistent with recent animal data that COX-2 inhibitor rofecoxib can suppress intestinal polyposis (21). It was reported earlier that the proinflammatory, pro-oncogenic protein COX-2 is markedly induced in the *Apc* ^{Δ 716} polyps at an early stage of polyp development, and that inhibition of COX-2 in the *Apc* ^{Δ 716} mouse, either by gene knockout or by specific inhibitors, can suppress intestinal polyposis (16, 17, 22). These results opened the possibility that specific COX-2 inhibitors such as celecoxib and rofecoxib could be effective chemopreventive agents for human colon polyposis and cancer. In fact, celecoxib has been demonstrated to be effective in reducing the number and size of colonic polyps in FAP patients (19). Our results are consistent with those with celecoxib, although we have focused on the effects of rofecoxib on rectal polyps.

The major purpose of our study has been to evaluate the chemopreventive effects of a COX-2 inhibitor that could serve as an adjuvant therapy after subtotal colectomy. Proctocolectomy with ileoanal anastomosis has been accepted as the standard operation for FAP patients. However, the operation requires extremely complex procedures, and has a high incidence of postoperative complications, compared with colectomy with an ileorectal anastomosis. Moreover, this radical operation affects the stool habit of the patients and compromises their quality of life. If the patients are younger, it can even affect their psychological development. Because of these reasons, colectomy with ileorectal anastomosis is a preferable operation giving a satisfactory functional result. To monitor the possible development

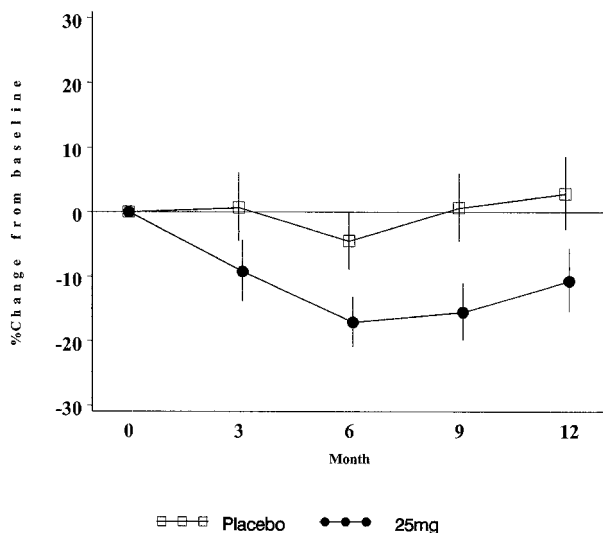


Fig. 2 Mean percentage of change from base line in the size of polyps; bars, \pm SE. At 9 months, the group given rofecoxib was associated with a significant reduction from the baseline in the size of rectal polyps as compared with the placebo group (-16.2% versus 1.5% ; $P < 0.001$).

of rectal carcinoma after surgery, it is important to continue periodic follow-up of the remaining rectum (23).

The possible use of rofecoxib to control the remaining rectal polyps in FAP patients was the motivation for this study. Long-term use of rofecoxib is well tolerated and provided efficacy that is comparable with that of a conventional NSAID in osteoarthritis (24). A large study demonstrated that rofecoxib is associated with significantly fewer clinically important upper gastrointestinal side effects than conventional NSAIDs (25). In the current study, the maximum reduction in the number of polyps was observed after 9 months of treatment with rofecoxib, whereas the slight relapse of rectal polyps was seen 3 months after completion of the rofecoxib treatment. It is important to note that no severe side effects were reported during the 9-month treatment period.

In conclusion, we have demonstrated that COX-2-specific inhibitors, such as rofecoxib, can help suppress the progression of colorectal polyps in FAP patients. If it is possible to prevent the development of rectal polyps and their progression to malignancy with chemotherapy with COX-2 inhibitors, then clearly the clinical benefits to patients with FAP would be considerable. Our data, although limited to the assessment of the polyps in the rectum, are encouraging and open the possibility of this adjuvant therapy for many patients with FAP.

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Clinical Cancer Research

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