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

Tetsuro Higuchi, Takeo Iwama, Keigo Yoshinaga, Masahiro Toyooka, Makoto M. Taketo, and Kenichi Sugihara

Department of Digestive Surgery, Graduate School, Tokyo Medical and Dental University, Tokyo 113-8519 [T. H., K. Y. M. T., K. S.]; Department of Pharmacology, Graduate School of Medicine, Kyoto University, Kyoto 606-8501 [M. M. T.]; and Department of Surgery, Kyoudo Hospital, Sasaki Institute, Tokyo 101-0062 [T. I.], Japan

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

INTRODUCTION

FAP is an autosomal dominant disease caused by a germ-line 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.

2 The abbreviations used are: FAP, familial adenomatous polyposis; APC, adenomatous polyposis coli; NSAID, nonsteroidal anti-inflammatory drug; COX, cyclooxygenase.
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 Kyoudo Hospital Sasaki Institute, (Tokyo, Japan) and Tokyo Medical and Dental University. Patients diagnosed as FAP on the basis of having at least 100 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 rectal region was still intact. Accordingly, patients with at

<table>
<thead>
<tr>
<th>Table 1 Schedule of the study</th>
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<tbody>
<tr>
<td>Months</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Colonoscopy</td>
</tr>
<tr>
<td>Gastroduodenoscopy</td>
</tr>
<tr>
<td>Physical examination</td>
</tr>
<tr>
<td>Blood pressure, body weight</td>
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<tr>
<td>Laboratory tests</td>
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</table>

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.
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 in the decrease in the number of polyps between the rofecoxib and placebo groups was statistically significant (P = 0.004). 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.

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

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Table 2 Baseline characteristics of the patients with familial adenomatous polyposis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo n = 9</th>
<th>Rofecoxib n = 12</th>
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<tbody>
<tr>
<td>Age yr.</td>
<td>33.6 ± 14.8</td>
<td>32.3 ± 11.2</td>
</tr>
<tr>
<td>Gender no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4 (44.4)</td>
<td>7 (58.3)</td>
</tr>
<tr>
<td>Female</td>
<td>5 (55.6)</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>Height cm</td>
<td>161.2 ± 7.2</td>
<td>162.7 ± 4.5</td>
</tr>
<tr>
<td>Weight kg</td>
<td>57.7 ± 12.9</td>
<td>51.8 ± 7.4</td>
</tr>
<tr>
<td>Surgical status no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact colon</td>
<td>3 (33.3)</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>Colectomy</td>
<td>6 (66.7)</td>
<td>7 (58.3)</td>
</tr>
<tr>
<td>No. of polyps</td>
<td>7.2 ± 3.3</td>
<td>8.0 ± 4.5</td>
</tr>
<tr>
<td>Polyp size mm</td>
<td>3.3 ± 0.8</td>
<td>3.0 ± 0.7</td>
</tr>
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*Plus-minus values are means ± SD.
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. The possible use of rofecoxib to control the remaining rectal polyps in FAP patients is the motivation for this study.

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REFERENCES

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