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Randomized Double-Blind Trial of Sulindac and Etodolac to Eradicate Aberrant Crypt Foci and to Prevent Sporadic Colorectal Polyps

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Abstract

Purpose: On the basis of the results of our preliminary trial suggesting that aberrant crypt foci (ACF) could be eradicated by short-term administration of sulindac, in the present study, we explored the feasibility of using ACF as surrogate markers for chemoprevention of colorectal cancer.

Experimental design: Randomly assigned to sulindac (300 mg daily), etodolac (400 mg daily), and placebo groups were 189 subjects without polyps or who had undergone polypectomy. Drugs were administered for 2 months. ACF in the rectal region were counted by magnifying endoscopy. Occurrence of polyps was evaluated at 12 months. A planned interim analysis was conducted.

Results: ACF number at 2 months was significantly suppressed in the sulindac group ($P = 0.0075$), but not in the etodolac group ($P = 0.73$). In the sulindac group, the numbers of adenomas plus hyperplastic polyps (total polyps) and adenomas at 12 months were significantly ($P = 0.02$) and marginally ($P = 0.064$) lower, respectively, in comparison with the placebo group; no such difference was observed in the etodolac group. In analysis of only polypectomized subjects, the numbers of total polyps and adenomas in the sulindac group were even more markedly lower, with P values of 0.014 and 0.034, respectively. A similar tendency was confirmed by analyses of the incidence of polyps at 12 months. Suppression rates of total polyps and adenomas in ACF responders to sulindac were significantly greater than in nonresponders. In all groups, compliance was more than 90% and no intolerable adverse effects were observed.

Conclusions: ACF may be useful as surrogate lesions for chemoprevention of colorectal cancer. *Clin Cancer Res; 17(11); 3803–11. ©2011 AACR.*

Introduction

Despite the recent introduction of various therapeutic modalities, colorectal cancer remains one of the most common causes of cancer deaths worldwide (1–3). Several chemopreventive modalities have been introduced in the past decade or so, and agents such as calcium (4), cyclooxygenase-2 (COX-2) inhibitors (5,6), aspirin (7–9), and sulindac, a nonsteroidal anti-inflammatory drug (NSAID; ref. 10), have been shown to inhibit the recurrence of colorectal polyps after polypectomy or the development of colorectal polyps. A major obstacle in the development of chemopreventive drugs is that they are administered for relatively long periods to cancer-free subjects; therefore, poor compliance and adverse effects frequently hamper trials.

We previously showed that aberrant crypt foci (ACF), tiny lesions that expressed the K-ras mutation and are identifiable only by magnifying endoscopy, correlated in number and size with the number of adenomas in patients with adenoma, and proposed these lesions to be precursors of colorectal adenoma and cancer (11–13). Subsequently, several investigators have confirmed our proposal of the ACF-adenoma-carcinoma sequence through demonstrating a close relationship between ACF and adenomas or cancers in terms of number, size, and pathologic features (14–19).

We then, though preliminarily, showed that ACF could be eradicated by short-term administration of sulindac (20,21) and proposed the possibility that discontinuous use of the drug may be just as effective as continuous use and may make the daunting task of chemoprevention more realistic. However, results of multicenter trials of

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Online registry: http://upload.umin.ac.jp; clinical trial no. C000000100.

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Translational Relevance

Trials for chemoprevention of cancer are generally daunting because drugs are administered for years to cancer-free subjects, resulting in low compliance and are sometimes associated with adverse effects. In the present randomized controlled study of chemoprevention of colorectal cancer, we successfully showed that a short-term (2 months) administration of a nonsteroidal anti-inflammatory drug (sulindac) to eradicate aberrant crypt foci, minute precursor lesions of polyps, was as effective as long-term administration of similar drugs in previously reported trials by using polyps as a surrogate marker for colorectal cancer. The results therefore suggest that a short-term and discontinuous administration of drugs is pertinent for chemoprevention because every cancer should be derived from precursor lesions (seeds), which could be readily eradicated by drugs.

chemoprevention by others have raised controversy over the ACF-adenoma-carcinoma sequence theory or the use of ACF as biomarkers for recurrent colorectal adenomas (22, 23). Results showed dissociation of ACF prevalence and adenoma history (22) or no significant modulation of ACF by celecoxib (23). However, accuracy as to the technical aspects of ACF detection in these studies might be questioned because the number of ACF detected was very low compared with that in other reports and inter-rater agreement rates were also low (11,14,15). Further, utilizing a COX-2 inhibitor might not have been appropriate in a trial to examine the effect on ACF because COX-2 was mostly negative in ACF and became positive in adenoma, although COX-1 was expressed in both ACF and adenoma (24).

In the present randomized controlled trial, to directly validate the usefulness of ACF as a surrogate marker for chemoprevention and to address the controversial issues described above, we explored the effect of short-term (2 months) administration of sulindac, an inhibitor of both COX-1 and COX-2, or etodolac, a selective COX-2 inhibitor, on ACF by employing magnifying endoscopy, which is a suitable method for detection of ACF as we reported previously (11,12). We also elucidated the relevancy of the effects of the drugs on ACF to that on polyp development 1 year after the start of the study.

Patients and Methods

Study design and subjects

This randomized, double-blinded, and placebo-controlled study was conducted between February 2002 and October 2007 at the 4th Department of Internal Medicine, Sapporo Medical University Hospital and its 4 affiliate hospitals. Actual recruitment was carried out from 2002 to 2006. The rather long-term recruitment period was because of the delay in approval by the institutional review board in 3 hospitals and the delay in dispensing the drug to 1 hospital. According to reduction rates in ACF number by sulindac administration in our preliminary trials (20, 21), we estimated that 360 subjects would generate 90% power for a difference in the ACF number among the groups. Because it was possible that the estimate of an adequate sample size to show significant efficacy of the investigational drug was too conservative, a planned interim analysis was carried out when half of the subjects had been enrolled.

Subjects were recruited from patients who had undergone colonoscopy for abdominal symptoms including discomfort, distension, and a feeling of tightness on defecation. Eligible criteria were (i) positive for ACF in the lower rectal region from the middle Houston valve to the dentate line, (ii) age from 20 to 75 years, (iii) no colorectal polyps or polyps had been resected by polypectomy, (iv) not pregnant, (v) no malignant disease, (vi) no active infection, (vii) no history of gastroduodenal ulcer, (viii) no use of NSAIDs or aspirin in the previous 2 months, (ix) no abnormal findings by laboratory tests [blood cell count, aspartate amino transferase, alanine aminotransferase (ALT), total protein, albumin, blood urea nitrogen, creatinine, total bilirubin, lactate dehydrogenase, creatine kinase, and electrolytes (Na, K, Cl)], and (x) no familial adenomatous polyposis.

Subjects were randomly assigned to 1 of the 3 treatment groups at a 1:1:1 ratio (sulindac, etodolac, or placebo) by an independent statistician in the study center. We administered each drug for only 2 months on the basis of our unpublished observation in the preliminary open trial, which showed that administration of sulindac brought about a significant reduction in ACF number in 6 of 7 patients with 2 months treatment, in 4 of 4 patients with 3 months of treatment, and in 5 of 5 with 5 months treatment, whereas in 6 patients with 1 month of treatment, the reduction rate was not significant. Therefore, in this study, the number of ACF was assessed after 2 months of drug administration (primary endpoint). The participants did not receive any further treatment, and assessment was made for the occurrence of polyps 1 year after initiation of the study (secondary endpoint).

There are reportedly 2 types of ACF, dysplastic, and non-dysplastic ACF, with the former type being suggested to be more likely a precursor of polyps than the latter (11, 17). However, in the present investigation, it was impossible to analyze these 2 types separately because the proportion of the dysplastic type among all ACF was too small for statistical analysis.

At the start of the study, we carried out a baseline colonoscopy on all patients to determine the presence of polyps in the entire colorectum and to count ACF in the rectal area. After 2 months of drug administration, we conducted only rectosigmoidoscopy on these patients to determine the number of ACF in the rectal area because the number of ACF in the rectal region correlates well with that in the total colorectum (11).

All patients provided written informed consent. The protocol and informed consent forms were approved

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by the institutional review board at each participating institution.

Endoscopy

Magnifying endoscopy (model EZW450, Fujinon-Toshiba ES System Co.) was used throughout the examination as previously reported (11, 12). The day before endoscopy, the patients consumed a low-residue diet, and were given orally 4 g magnesium sulfate and 5 mg of sodium picosulfate. On the day of endoscopy, 2,000 mL of polyethylene glycol (PEG) was given orally. When the feces were not sufficiently clear, they were given another 1,000–2,000 mL of PEG to ensure sufficient bowel cleansing.

A total of 5 endoscopists from Muroran Shinnittesu Hospital, Otaru Ekisaikai Hospital, Gorinbashi Hospital, and Sapporo Cancer Center Hospital, were engaged in the endoscopic examinations. They were all trained for at least 1 month at the 4th Department of Sapporo Medical University Hospital for detection of ACF. They were all blinded to the treatment arms. Each endoscopist carried out almost the same number of examinations in each arm.

At the baseline colonoscopy, the endoscope was inserted into the cecum, and the entire colorectum was carefully observed as the endoscope was pulled back. Insertion into the cecum was verified by videotape as described below. When the endoscope was pulled back to the rectum, the lower rectal region from the middle Houston valve to the dentate line was washed thoroughly with water, sprayed with 0.25% methylene blue, which was left to stand for 2 minutes, then washed again thoroughly with water. The number of ACF in the rectal region, which has been shown to correlate with that in entire colon (11), was counted by magnifying endoscope.

For the 2-month survey for ACF by rectosigmoidoscopy, we simply used a 110 mL glycerin enema to cleanse the region, and if the rectum was not sufficiently cleansed, the subject was orally administered 2,000–4,000 mL PEG.

One year after the initiation of the study, all patients underwent total colonoscopy to detect polyps in the entire colorectum. The same cleansing preparation was used as for the baseline colonoscopy. The same endoscopist carried out the baseline, 2-month, and 1-year endoscopic examinations for each subject. All procedures were recorded on videotape, and all ACF and polyps were photographed. The numbers of ACF and polyps were first counted by the operators during performance of the colonoscopy or rectosigmoidoscopy. To further ensure validity, another count was made through observation of the recorded videotapes by 3 expert endoscopists (M.M., Y.N., and Y.T.) from the Assessment Panel of Endoscopy.

Drug administration and monitoring for adverse effects

For blinding of subjects and trial staff, identical looking capsules were filled with either 150 mg of sulindac (Banyu, Tokyo, and Japan), 200 mg of etodolac (Wyeth Pharmaceutical Co. Ltd.), or 200 mg of lactose as the placebo. All subjects were also administered 15 mg of lansoplazole twice daily. The drug set for each subject was labeled by an identification code unrelated to the allocation to conceal the allocation from subjects and trial staff until the blind was opened.

Subjects were instructed to take 1 capsule after food in the morning and 1 capsule after food in the evening. Study patients visited the hospital every 2 to 4 weeks to be evaluated for subjective symptoms of any adverse events, including abdominal and cardiovascular symptoms and to receive a new supply of medication. Two weeks after initiation of the treatment, liver and renal function was evaluated. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) Version 2.0. Compliance was monitored by counting the capsules returned by patients every month at outpatient clinic. A Safety Monitoring Board reviewed the study semi-annually.

Statistical analysis

To maintain the overall type I error rate at 5%, Pocock's method (25) was applied for the interim analysis with a significance level of 0.0294. The number of ACF, the primary endpoint, was compared by the Mann–Whitney *U* test. For adjustment of multiplicity of 2 times pairwise comparison (placebo versus sulindac and placebo versus etodolac), the level of significance (0.0294) was modified by Bonferroni's method, that is, $0.0294/2 = 0.0147$. The number of polyps after 1 year was compared by Mann–Whitney *U* test. A comparison of the incidence of polyps after 1 year was made according to logistic regression analysis, and the level of significance was also set at $P = 0.0147$.

Results

Patients

A total of 304 subjects were screened for eligibility, and 115 subjects were excluded from the study for the reasons shown in Figure 1. The remaining 189 patients underwent randomization: 63 were assigned to the sulindac group, 64 to the etodolac group, and 62 to the placebo group (Fig. 1). Of these, 10 subjects withdrew their informed consent within 2 weeks: 5 after consulting with their family at home, 4 after deep reconsideration, and 1 after consultation with a supervisor at work. These subjects did not allow use of their data. Of the remaining 179, 4 were dropped from the study for taking NSAIDs for common cold, 1 for taking aspirin for headache, and 1 because of having orthopedic surgery during the study. The 177 patients (59, sulindac group; 60, etodolac group; 58, placebo group) underwent the 2-month endoscopy. The analysis was based on the intent-to-treat principle. Table 1 shows baseline characteristics of the subjects. No particular difference in each characteristic among the 3 groups was observed. In all groups, the number of polypectomized subjects was almost 5 times that of polyp-free subjects. No patient with hereditary nonpolyposis colorectal cancer (HNPCC) was included when we reviewed the subjects with regard to diagnostic criteria for HNPCC.

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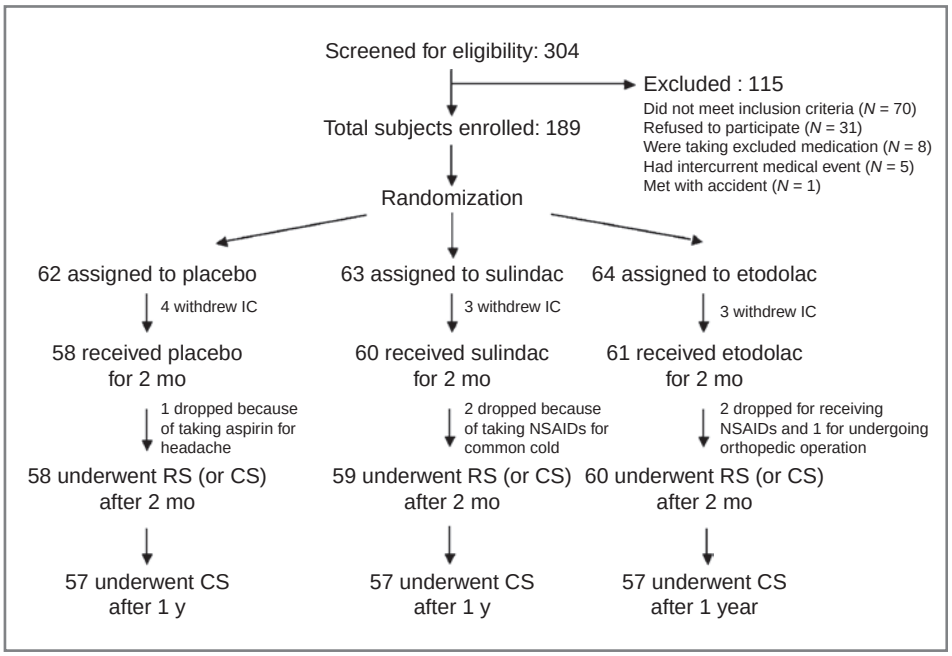

Figure 1. Trial profile. A total of 304 patients were screened for eligibility, and 115 were excluded. Enrolled were 189 patients who were randomly assigned to either the sulindac, etodolac, or placebo group. Drugs were administered for only 2 months, and the number of rectal ACF was assessed by rectosigmoidoscopy (RS). One year after the initiation of treatment, subjects underwent total colonoscopy (CS) to detect all polyps in the entire colorectum. The number of subjects is based on the intent-to-treat (ITT) population.

Validity of endoscopic assessment of ACF

The number of ACF in 26 patients randomly selected was evaluated through review of videotapes independently by 3 endoscopists from the Assessment Panel of Endoscopy (M. M., Y.N., and Y.T.) to assess the degree of concordance with the endoscopic findings. The mean counts of ACF were 8.5 ± 3.7 for M.M., 8.8 ± 4.6 for Y.N., and 8.6 ± 3.9 for Y.T. The inter-rater agreement rates within +/− 1 ACF between M.M. and Y.N., M.M. and Y.T., and Y.N. and Y.T. were 88.5%, 84.6%, and 92.3%, respectively. The Cronbach's alpha was 0.89, proving the validity of the endoscopic count of ACF.

Number of ACF before and after the 2-month treatment

The number of ACF before and after the 2-month treatment period in the 3 groups is shown in Table 2. In the polypectomized subjects, the ACF number after 2 months in the sulindac group was significantly lower than that in the placebo group ($P < 0.001$), whereas the number in the

Table 1. Baseline characteristics of subjects

	Placebo ($n = 58$)	Sulindac ($n = 60$)	Etodolac ($n = 61$)
Age, (mean ± SD), y	64.0 ± 9.9	65.8 ± 10.2	63.1 ± 9.7
Sex (M/F)	36/22	36/24	37/26
Colorectal cancer in parent no. (%)	8 (13.8)	8 (13.3)	10 (16.4)
Current smoker, no. (%)	11 (19.0)	12 (20.0)	11 (18.0)
History of diabetes, no. (%)[a]	5 (8.6)	6 (10.0)	5 (8.2)
History of hyperlipidemia, no. (%)[b]	14 (24.1)	15 (25.0)	16 (26.2)
History of hypertension, no. (%)[c]	18 (31.0)	20 (33.3)	18 (29.5)
Findings at baseline CS			
No. of polyps, median (interquartile range)	1.0 (0.5–2.0)	1.0 (0.0–2.0)	1.0 (0.0–2.0)
No. of adenomas, median (interquartile range)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	1.0 (0.0–2.0)
Polypectomy/polyp-free subjects	48/10	50/10	50/11

[a]History of diabetes was defined as use of antidiabetic medication or participant report of clinically diagnosed diabetes.
[b]History of hyperlipidemia was defined as use of cholesterol-lowering medication or participant report of clinically diagnosed hyperlipidemina.
[c]History of hypertension was defined as use of antihypertensive medication or participant report of clinically diagnosed high blood pressure.

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Table 2. Comparison of ACF number among the sulindac, etodolac, and placebo groups before and after treatment

	Before[a]	After 2 mo	
Subjects with polypectomy			
Placebo			
Mean ± SD	7.77 ± 4.66	6.87 ± 6.03	
Median (interquartile range)	7.0 (5.0–10.0)	6.0 (3.0–8.5)	
Sulindac			$P < 0.001$[b]
Mean ± SD	7.70 ± 4.04	4.00 ± 2.95	
Median (interquartile range)	7.0 (4.5–10.0)	4.0 (1.0–6.0)	
Etodolac			
Mean ± SD	7.52 ± 4.01	6.28 ± 5.21	$P = 0.67$
Median (interquartile range)	7.0 (4.0–10.0)	5.0 (2.5–8.5)	
Polyp-free subjects			
Placebo			
Mean ± SD	4.00 ± 1.82	3.90 ± 2.72	
Median (interquartile range)	4.0 (2.0–6.0)	3.0 (1.0–7.0)	
Sulindac			$P = 0.38$
Mean ± SD	4.40 ±2.21	2.70 ±2.16	
Median (interquartile range)	4.0 (2.0–6.0)	3.0 (0–4.5)	
Etodolac			
Mean ± SD	4.73 ± 2.32	4.10 ± 2.60	$P = 0.54$
Median (interquartile range)	4.0 (0–5.5)	4.0 (2.0–9.0)	
Ali subjects			
Placebo			
Mean ± SD	7.12 ± 4.53	6.35 ± 5.69	
Median (interquartile range)	6.5 (4.0–9.0)	5.0 (2.3–8.0)	
Sulindac			$P = 0.0075$[b]
Mean ± SD	7.15 ± 3.98	3.77 ± 2.86	
Median (interquartile range)	6.5 (4.0–9.0)	4.0 (1.0–5.3)	
Etodolac			
Mean ± SD	7.01 ± 3.89	5.91 ± 4.93	$P = 0.73$
Median (interquartile range)	6.0 (4.0–9.0)	5.0 (2.0–7.5)	

[a] There were no significant differences before treatment among the 3 groups by the Kruskal-Wallis test.
[b] Significant *P* value by Mann–Whitney *U* test.

etodolac group was not significantly different from the placebo group ($P = 0.67$). Among polyp-free subjects, neither the sulindac nor etodolac group had a significant reduction in ACF compared with the placebo group. When polypectomized and polyp-free subjects were combined in the analysis, results were similar to those in the polypectomized subjects with a significant suppression of ACF ($P = 0.0075$) only in the sulindac group, reflecting the fact that polypectomized subjects were dominant in the subject population. Intraindividual comparison in ACF numbers before and after treatment (Supplementary Table S1) also showed a significant decrement in ACF in the sulindac group of polypectomized subjects ($P < 0.001$) as well as in all subjects in the sulindac group ($P < 0.001$). In the analysis of subjects receiving etodolac, ACF number tended to decline slightly after 2 months but without significance ($P = 0.09$). Thus, because the superiority of the test drug (sulindac) over the placebo was confirmed, termination of the study was recommended by the Data Monitoring Board. Incidentally, before the treatment, ACF number in subjects who had adenoma (subjects with polypectomy) was significantly higher than that in the subjects without adenoma (polyp-free subjects) in each group ($P < 0.001$), which was in good agreement with our previous finding (10).

Number and incidence of total polyps and adenomas 1 year after treatment

A total of 107 polyps were found after 1 year. Of these, 96 were adenomas and 11 were hyperplastic polyps (Supplementary Table S2). There was no significant difference in location and histology among the 3 groups. The average size in the sulindac group was slightly smaller than in the placebo group ($P = 0.16$ by Mann–Whitney *U* test).

In polypectomized subjects, the mean numbers of total polyps (adenoma plus hyperplastic polyp) and adenomas

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Table 3. Numbers of total polyps and adenomas 1 year after initiation of treatment

	Placebo	Sulindac	Etodolac
Subjects with polypectomy	$n = 48$	$n = 48$	$n = 47$
No. of total polyps			
Mean ± SD	0.92 ± 1.05	0.42 ± 0.68	0.73 ± 0.94
Median (range)	1 (0–4)	0 (0–2)	0 (0–3)
P value		$P = 0.014$[a]	$P = 0.64$
No. of adenomas			
Mean ± SD	0.81 ±1.0	0.42 ± 0.71	0.68 ± 0.86
Median (range)	1 (0–4)	0 (0–2)	0 (0–3)
P value		$P = 0.034$	$P = 0.61$
Polyp-free subjects	$n = 9$	$n = 9$	$n = 10$
No. of total polyps			
Mean ± SD	0.22 ± 0.44	0.22 ± 0.44	0.20 ± 0.42
Median (range)	0 (0–1)	0 (0–1)	0 (0–1)
P value		$P = 1.00$	$P = 0.94$
No. of adenomas			
Mean ± SD	0.11 ±0.33	0.22 ± 0.44	0.20 ± 0.67
Median (range)	0 (0–1)	0 (0–1)	0 (0–2)
P value		$P = 0.54$	$P = 0.93$
All subjects	$n = 57$	$n = 57$	$n = 57$
No. of total polyps			
Mean ± SD	0.81 ± 1.01	0.40 ± 0.70	0.68 ± 0.89
Median (range)	0 (0–4)	0 (0–2)	0 (0–3)
P value		$P = 0.020$	$P = 0.61$
No. of adenomas			
Mean ± SD	0.70 ± 0.96	0.39 ± 0.68	0.60 ± 0.84
Median (range)	0 (0–4)	0 (0–2)	0 (0–3)
P value		$P = 0.064$	$P = 0.63$

[a]Significant *P* value by Mann–Whitney *U* test.

in the sulindac group were significantly ($P = 0.014$) and marginally ($P = 0.034$) lower, respectively, whereas those in the etodolac group were not lower with statistical significance ($P = 0.64$ for total polyps and $P = 0.61$ for adenomas) in comparison with the placebo group (Table 3). In polyp-free subjects, neither total polyp number nor adenoma number was lower in either the sulindac or etodolac group compared with the placebo group. In analyses of all subjects (polypectomized plus polyp-free subjects), the numbers of total polyps and adenomas were markedly ($P = 0.020$) and marginally ($P = 0.064$) lower in the sulindac group but not in the etodolac group. The incidences of total polyps and adenomas in polypectomized subjects were markedly ($P = 0.025$) and marginally ($P = 0.039$), respectively, lower in the sulindac group but not in the etodolac group in comparison with the placebo group (Table 4). In polyp-free subjects, there were no differences in incidence among the groups. When incidence was analyzed in all subjects, the incidence of total polyps was marginally lower ($P = 0.037$) and that of adenomas tended to be lower ($P = 0.08$) in the sulindac group but not in the etodolac group. Though statistically not significant because of the small number for analysis, there was a tendency ($P = 0.25$) for the incidence of multiple adenomas to decrease by treatment with sulindac; however, there were no apparent differences between the etodolac and placebo groups ($P = 0.81$).

Comparison of number and incidence of total polyps and adenomas between ACF responders and nonresponders to drugs

We selected out as responders those subjects whose ACF number became zero at 2 months or whose ACF reduction rate by 2 months was above the 90th percentile of the placebo group. We then compared polyp number and incidence at 12 months of the responders with those in the remaining subjects, which were designated as "nonresponders" (Supplementary Table S3). In the sulindac group, the numbers of total polyps and adenomas in responders were significantly lower than in nonresponders ($P = 0.017$ and $P = 0.023$, respectively). Moreover, the incidences of total polyps and adenomas in responders

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Table 4. Incidence of total polyps and adenomas 1 year after treatment

	Placebo	Sulindac	Etodolac
Subjects with polypectomy	$n = 48$	$n = 48$	$n = 47$
Incidence of total polyps	26/48 (54.2%)	15/48 (31.3%)	24/47 (46.8%)
Risk ratio (95% CI)		0.39 (0.17–0.89)	0.96 (0.43–2.15)
P value[a]		0.025	0.92
Incidence of adenomas	24/48 (50.0%)	14/48 (29.2%)	21/47 (44.7%)
Risk ratio (95% CI)		0.41 (0.18–0.96)	0.81 (0.36–1.81)
P value[a]		0.039	0.60
Polyp-free subjects	$n = 9$	$n = 9$	$n = 10$
Incidence of total polyps	2/9 (22.2%)	2/9 (22.2%)	2/10 (20.0%)
Risk ratio (95% CI)		1.00 (0.11–9.23)	0.88 (0.10–7.95)
P value[a]		1.00	0.91
Incidence of adenomas	1/9 (11.1%)	2/9 (22.2%)	2/10 (20.0%)
Risk ratio (95% CI)		2.29 (0.17–31.0)	2.00 (0.15–26.7)
P value[a]		0.53	0.60
All subjects	$n = 57$	$n = 57$	$n = 57$
Incidence of total polyps	28/57 (49.1%)	17/57 (29.3%)	26/57 (45.6%)
Risk ratio (95% CI)		0.44 (0.20–0.95)	0.87 (0.42–1.81)
P value[a]		0.037	0.71
Incidence of adenomas	25/57 (43.9%)	16/57 (28.1%)	23/57 (40.4%)
Risk ratio (95% CI)		0.50 (0.23–1.09)	0.87 (0.41–1.82)
P value[a]		0.08	0.70

[a]Logistic regression analysis was used to calculate *P* values.

were significantly lower than in nonresponders ($P = 0.011$ and $P = 0.022$, respectively). A similar tendency was observed but not with significance in the etodolac group.

Adverse effects and compliance

The incidence of adverse events, including symptoms such as abdominal pain, heartburn, diarrhea, and exanthema, and abnormal laboratory test results such as a transient elevation of ALT or creatinine was less than 4% (Table 5); all were grade 1. Differences were not significant among the 3 groups. No cardiovascular events, including myocardial infarction, angina, stroke, and transient ischemic attacks, were observed during the 2 months of treatment. Average compliance with medication was 92.7%: 93.9% in the placebo group, 91.7% in the sulindac group, and 92.5% in the etodolac group.

Discussion

For the present study, we selected 2 types of drugs, a NSAID (sulindac) and a COX-2 inhibitor (etodolac) because both were proved to be effective as chemopreventive agents for colon adenoma (10, 26–28). Drug dosages were selected according to information in previous reports (11, 29). Although one of the COX-2 inhibitors, high-dose celecoxib, was reported to increase the risk of cardiovascular events (30), we considered that our protocol, using etodolac in 1 arm, was safe because the cardiac adverse event related to etodolac was reportedly negligible at the dosage we used (31). We administered lansoprazole to all subjects, including those in the placebo group, to prevent any possible gastrointestinal damage caused by sulindac or etodolac.

In most previous chemopreventive trials for colon cancer, only the polypectomized subjects were enrolled (4–9). In the present trial, we recruited both polypectomized and polyp-free subjects in view of the possibility of differences between the 2 subject groups in sensitivity of ACF and polyps to drugs. However, to our disappointment, the number of polyp-free subjects enrolled was so small that we were, practically, not able to draw any meaningful conclusion from comparisons of these 2 groups. Incidentally, a possible reason for the high rate of polyps detected by the baseline colonoscopy was because patients who underwent the colonoscopic examination were those at high risk for colorectal polyps, such as those with fecal occult blood. Further, the relatively high proportion of polypectomized subjects compared with polyp-free subjects was probably because of their higher motivation to participate in the current trial. Nevertheless, the results of the 2-month treatment on ACF both in comparison analysis among groups (Table 2) and in the intragroup analysis (Supplementary Table S1) clearly indicated the effectiveness of sulindac in eradicating the lesions, particularly in polypectomized subjects. Thus, the primary endpoint of the present study was achieved. The failure of etodolac to eradicate ACF is probably explained by the fact that most ACF do not express COX-2 (20). Moreover, it is surmised

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Table 5. Incidence of adverse events and compliance

	Total $n = 179$	Placebo $n = 58$	Sulindac $n = 60$	Etodolac $n = 61$
Adverse events				
Abdominal pain	5 (3.0%)	2 (3.4%)	2 (3.3%)	1 (1.6%)
Heartburn	2 (1.1%)	1 (1.7%)	0 (0%)	1 (1.6%)
Diarrhea	2 (1.1%)	1 (1.7%)	1 (1.7%)	0 (0%)
Exanthema	1 (0.6%)	0 (0%)	1 (1.7%)	0 (0%)
Chest discomfort	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)
Liver dysfunction[a]	2 (1.1%)	1 (1.7%)	0 (0%)	1 (1.6%)
Renal dysfunction[b]	2 (1.1%)	0 (0%)	1 (1.7%)	1 (1.6%)
Average compliance	92.7%	93.9%	91.7%	92.5%

[a]Liver dysfunction was defined as ALT level greater than the upper limit of normal.
[b]Renal dysfunction was defined as creatinine level greater than the upper limit of normal.

that in short-term treatment etodolac, which could not eradicate ACF, was ineffective in suppressing polyp development whereas sulindac was able to inhibit incidence of polyp 1 year after the initiation of treatment by eradicating ACF with short-term treatment.

Incidentally, intragroup analysis showed that in the placebo and etodolac groups, there was a slight tendency of a decrease in ACF number after 2 months although without statistical significance. At present, this cannot be explained but it can be speculated that subjects in these groups, as well as in the sulindac group, became very conscious of their dietary habits after enrollment in the study, which somehow influenced ACF occurrence. In this respect, the analysis among groups may be more reliable than intragroup analysis.

As to the relevance of histology of ACF (dysplastic and nondysplastic ACF) to their development into adenoma, no conclusive result was obtained in this study because 2 histologic types of ACF could not be analyzed separately because of the small proportion of dysplastic ACF in the total ACF population.

Explanation of the relevance of the effect of the drug on ACF to that on polyp development was another important task of the present study. Results showing in both analyses of the number and incidence of adenoma or total polyps either a significant or marked (marginal) reduction in the sulindac group strongly suggest not only the effectiveness of short-term treatment with sulindac in suppressing polyp occurrence but also the utility of ACF as precursor lesions for polyps although the possibility that the reduction in ACF was indirectly related to that of polyp occurrence cannot be completely denied. This notion was further supported by results of the analysis of responders versus nonresponders that showed significantly fewer polyps in the former than in the latter subjects in the sulindac group. Moreover, the average polyp size in the sulindac group was smaller than in the placebo group, although without statistical significance. Further, when the incidence of multiple adenomas was selectively analyzed, though statistically not significant because of the small number of patients, there was some tendency toward a decrease after sulindac treatment ($P = 0.25$). This also supports the notion that by suppressing ACF with sulindac, subsequent occurrence of adenoma may be reduced. In addition, the finding that the difference between the incidence of adenoma in polypectomized subjects in the sulindac group (29.2%) and that in the placebo group (50.0%) was almost the same as in previous studies in which aspirin or NSAIDs were administered over a long-term (7–9) suggests the possibility that 2 months of treatment may be as potent as 1 or 2 years in terms of adenoma prevention. Nonetheless, the suppressive effect of sulindac on adenoma in both the present study and in previous studies was not very substantial, that is, an up to 40% to 50% suppression rate. Thus, a future task is to develop a more effective drug, such as a specific inhibitor of GST-pi, which we showed in our previous reports to be quite potent in eradicating ACF (20, 32). Incidentally, the relatively high polyp recurrence rate after 1 year (43.9%), in agreement with that of a recent report (44.6%; ref. 6), may be because of advancements in endoscopic technology.

In conclusion, our results indicate that ACF may be more advantageous as surrogate lesions than adenomas for chemoprevention of colorectal cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Randomized Double-Blind Trial of Sulindac and Etodolac to Eradicate Aberrant Crypt Foci and to Prevent Sporadic Colorectal Polyps

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