

Difluoromethylornithine Plus Sulindac for the Prevention of Sporadic Colorectal Adenomas: A Randomized Placebo-Controlled, Double-Blind Trial

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Abstract

Preclinical studies of chemoprevention drugs given in combination at low doses show remarkable efficacy in preventing adenomas with little additional toxicities, suggesting a strategy to improve risk to benefit ratios for preventing recurrent adenomas. Three hundred seventy-five patients with history of resected (≥ 3 mm) adenomas were randomly assigned to receive oral difluoromethylornithine (DFMO) 500 mg and sulindac 150 mg once daily or matched placebos for 36 months, stratified by use of low-dose aspirin (81 mg) at baseline and clinical site. Follow-up colonoscopy was done 3 years after randomization or off-study. Colorectal adenoma recurrence was compared among the groups with log-binomial regression. Comparing the outcome in patients receiving placebos to those receiving active intervention, (a) the recurrence of one or more adenomas was 41.1% and 12.3% (risk ratio, 0.30; 95% confidence interval, 0.18-0.49; $P < 0.001$); (b) 8.5% had one or more advanced adenomas, compared with 0.7% of patients (risk ratio, 0.085; 95% confidence interval, 0.011-0.65; $P < 0.001$); and (c) 17 (13.2%) patients had multiple adenomas (>1) at the final colonoscopy, compared with 1 (0.7%; risk ratio, 0.055; 0.0074-0.41; $P < 0.001$). Serious adverse events (grade ≥ 3) occurred in 8.2% of patients in the placebo group, compared with 11% in the active intervention group ($P = 0.35$). There was no significant difference in the proportion of patients reporting hearing changes from baseline. Recurrent adenomatous polyps can be markedly reduced by a combination of low oral doses of DFMO and sulindac and with few side effects.

More than 50,000 people in the United States will die in 2007 from colorectal cancer. In the United States, cancer is the leading cause of death in people under age 74 years (1), and colorectal cancer is the second most common cause of cancer deaths after lung cancer (2). Colorectal cancer may be prevented by removal of precursor adenomas found during screening sig-

moidoscopy or colonoscopy (3), although rates are variable and range from 30% to 90% depending highly on reimbursement policies (4, 5).

Diet and inflammation have been associated with risk of colorectal cancer (6), and a series of clinical trials have been conducted to test the efficacy of individual dietary supplements or anti-inflammatory agents to prevent the incidence or recurrence of colon polyps (7-14). Unfortunately, these trials have not translated into significant changes in medical practice for prevention or management of colon cancer for a variety of reasons, including lack of efficacy, unacceptable toxicities, and the availability of competing strategies for risk reduction (15).

Studies in rodent models have shown that combination chemoprevention strategies are often more effective than those using individual agents (16, 17). Difluoromethylornithine (DFMO) has been identified as a potent inhibitor of intestinal and colon carcinogenesis in animal models, especially in combination with nonsteroidal anti-inflammatory drugs (18-20). DFMO and the nonsteroidal anti-inflammatory drug sulindac also interact additively to prevent the growth and viability of human colon cancer cells (21). The results of a phase III clinical chemoprevention trial evaluating the combination of DFMO and sulindac for the prevention of colon polyp recurrence are reported here.

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Materials and Methods

Study design

This study was a randomized, double-blind placebo-controlled trial to test whether the combination of a low dose of DFMO plus a low dose of sulindac reduces the recurrence of colorectal adenomas detected by standard colonoscopy. The trial involved seven clinical sites in the United States. The human subjects committee at each site approved the study protocol and written informed consent was provided by all patients before enrollment. Quality control to promote uniform practice and protocol compliance included meetings before enrollment and site inspections during and after the trial. An independent Data and Safety Monitoring Board reviewed safety and efficacy data twice yearly.

Recruitment and study population

Eligibility required patients of ages 40 to 80 years with a history of ≥ 1 resected adenoma of at least 3 mm within 5 y before study entry. A screening colonoscopy within 6 mo of study entry was done and all polyps removed and pathologically examined. A 1-mo placebo run-in period was used to assess compliance. Before randomization to the agents, pre-randomization screening was done and included baseline history, physical examination, pure-tone audiometry, and laboratory evaluations for baseline hematologic, renal, and hepatic status. Three years after randomization, colonoscopies were done. Gastroenterologists associated with the trial performed all study colonoscopies.

Subjects were ineligible if they had a history of familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, inflammatory bowel disease, or invasive cancer within 5 y before enrollment. Also ineligible were subjects with renal, hepatic, or bleeding disorders; subjects hypersensitive to selective inhibitors of cyclooxygenase-2, nonsteroidal anti-inflammatory drugs, salicylates, or sulfonamides; and subjects who had undergone large-bowel resection of >10 cm (excluding appendectomy). Participants with >20 dB uncorrectable hearing loss above age-adjusted norms (assessed by pure-tone audiometry) at any frequency in the normal hearing range were ineligible. To be randomized, participants had to show 80% adherence to the 1-mo run-in medication.

Safety evaluations during the study included physical examinations and laboratory evaluations at return visits after the run-in and 3, 6, 9, 12, and every 6 mo through the end of the study. Pure-tone audiograms were done at 18 and 36 mo or off-study, and repeated 6 mo later. Compliance with the protocol, including in-person and telephone visits, study medication, and blood draws, was monitored throughout the duration of the study.

Study treatment

DFMO was given orally at a dose of 500 mg and sulindac at a dose of 150 mg/d. The randomization used a blocked design and was stratified by clinical site and on the basis of the use (defined as ≤ 81 mg daily or ≤ 325 mg twice weekly) or nonuse of low-dose aspirin at study entry.

Assessment of end points, adverse events, and follow-up

The reports for all polyps removed during colonoscopies were submitted for central pathology review and the diagnosis of adenomas was confirmed using standard diagnostic criteria. Secondary efficacy end points included the number and size of colorectal adenomas and the total adenoma burden over the 3-y period. An additional a priori secondary end point was the detection of an advanced adenoma with any of the following characteristics: size of at least 1.0 cm by endoscopic measurements, villous or tubulovillous histologic features, high-grade dysplasia, and intramucosal or invasive carcinoma. Safety analyses were based on investigator-reported adverse events, serious adverse events, laboratory measurements, and physical examinations. Adverse events were coded according to the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) Body System.

Table 1. Baseline characteristics of the patients were evenly distributed between arms

Characteristic	Placebo (n = 184)	DFMO/sulindac (n = 191)
Age, y		
Median	60	60
Mean \pm SD	61 \pm 8.2	60 \pm 8.6
Range	42-78	41-79
Male sex, n (%)	138 (75.0)	147 (77.0)
Race or ethnic group, n (%)		
White	158 (85.9)	155 (81.2)
Black	6 (3.3)	10 (5.2)
Hispanic	12 (6.5)	14 (7.3)
Asian or Pacific Islander	4 (2.2)	9 (4.7)
Other	4 (2.2)	3 (1.6)
Body mass index (mean \pm SD)		
Men	28.4 \pm 4.5	29.2 \pm 5.5
Women	29.4 \pm 7.5	27.7 \pm 5.8
No. reported adenomas*	2.51 \pm 2.3	2.49 \pm 2.2
Largest adenoma ≥ 1 cm, n (%) [†]	40 (21.7)	38 (19.9)
Use of low-dose aspirin, n (%)	69 (37.5)	77 (40.3)
History of cardiovascular disease, n (%)	67/155 (43.2)	73/158 (46.2)
History of high blood pressure or hypertension, n (%) [‡]	47/155 (30.3)	48/158 (30.4)
History of diabetes, n (%) [‡]	21/151 (13.9)	25/152 (16.4)
Current or prior cigarette smoker, n (%) ^{‡,§}	41/99 (41.4)	42/100 (42.0)

*Placebo, n = 183; DFMO/sulindac, n = 189. Number of polyps reported as "multiple" for three patients.

[†]Adenoma is defined as tubular, tubulovillous, villous, cancer *in situ*, adenoma, or tubular adenoma with high-grade dysplasia.

[‡]The denominator is the number of subjects for whom information was recorded. Missing values are not included.

[§]Self-reported information.

Statistical analysis

Based on the two-sample test of binomial proportions, the trial was designed with a statistical power of 90% to detect a 50% decrease in the rate of recurrent adenomas experienced by the DFMO plus sulindac group, assuming a 35% cumulative incidence rate of adenomas in the placebo group, and 0.025 one-sided level of significance. Based on these assumptions, 292 subjects were required for end point evaluation. To account for a dropout rate of as much as 25%, a total of 375 subjects were randomized. The trial included a prespecified stopping rule allowing for early stopping in favor of efficacy or futility. Interim analyses were planned when $\sim 60\%$ and 80% of the maximal planned information for the trial were available. The stopping rule was chosen to maintain an overall one-sided type I error rate of 2.5%, using a one-sided O'Brien-Fleming (22) efficacy bound with a futility bound parameterized via the unified family of group sequential designs with $P = 0.9$ (23). Adjustments to the stopping rule to account for shifts in the actual timing of analyses while maintaining the desired type I error rate were done using the constrained boundaries method (24). Based on results observed at the second interim analysis, the Data Safety and Monitoring Board of the study recommended early termination

in favor of efficacy. Here we present the results of data on the final intention-to-treat cohort of 267 evaluable patients. For the primary efficacy analysis, bias-adjusted estimates of the difference in recurrence rates and corresponding repeated confidence intervals were computed to account for the stopping rule (25).

In patients treated with DFMO plus sulindac compared with those treated with placebo, the relative risks of recurrent adenomas and of the development of at least one advanced adenoma were assessed by log-binomial regression. Treatment groups were compared with regard to the estimated censoring distribution due to early treatment termination using the Kaplan-Meier method. Investigator-reported adverse events were analyzed in total and according to prespecified categories to describe gastrointestinal, hematologic, and cardiovascular disorders; ototoxicity; and hospitalizations. The analyses included all events occurring after the first dose of study medication. The relative risk of hearing loss of at least 15 dB was assessed by log-binomial regression.

Results

Baseline characteristics

Baseline variables were similar across the two treatment groups (Table 1). Patient characteristics included age, gender,

race/ethnicity, body mass index, colorectal cancer risk factors, prior use of low-dose aspirin, history of diabetes, hypertension, cardiovascular events, current smoking status, and colorectal cancer risk factors (i.e., number and characteristics of prestudy polyps).

Subject disposition

The study schema, presented in Fig. 1, indicates the number of patients randomized to treatment groups, the number of patients with data included in the final analyses, and the number of patients who had colonoscopies at time points other than between the 33- and 39-month window and timing of follow-up colonoscopies. Adherence to the treatment regimen was adequate. Seventy percent of patients in both groups adhered to the active intervention from 50% to 90% of the time. Twenty-five percent of patients adhered to the active intervention at least 90% of the time compared with 24% of patients receiving placebos.

After the first interim analysis (60% of patients completed the 3-y colonoscopy follow up), the Data and Safety Monitoring Board endorsed an accelerated analysis, following which the trial was stopped with appropriate follow-up of the

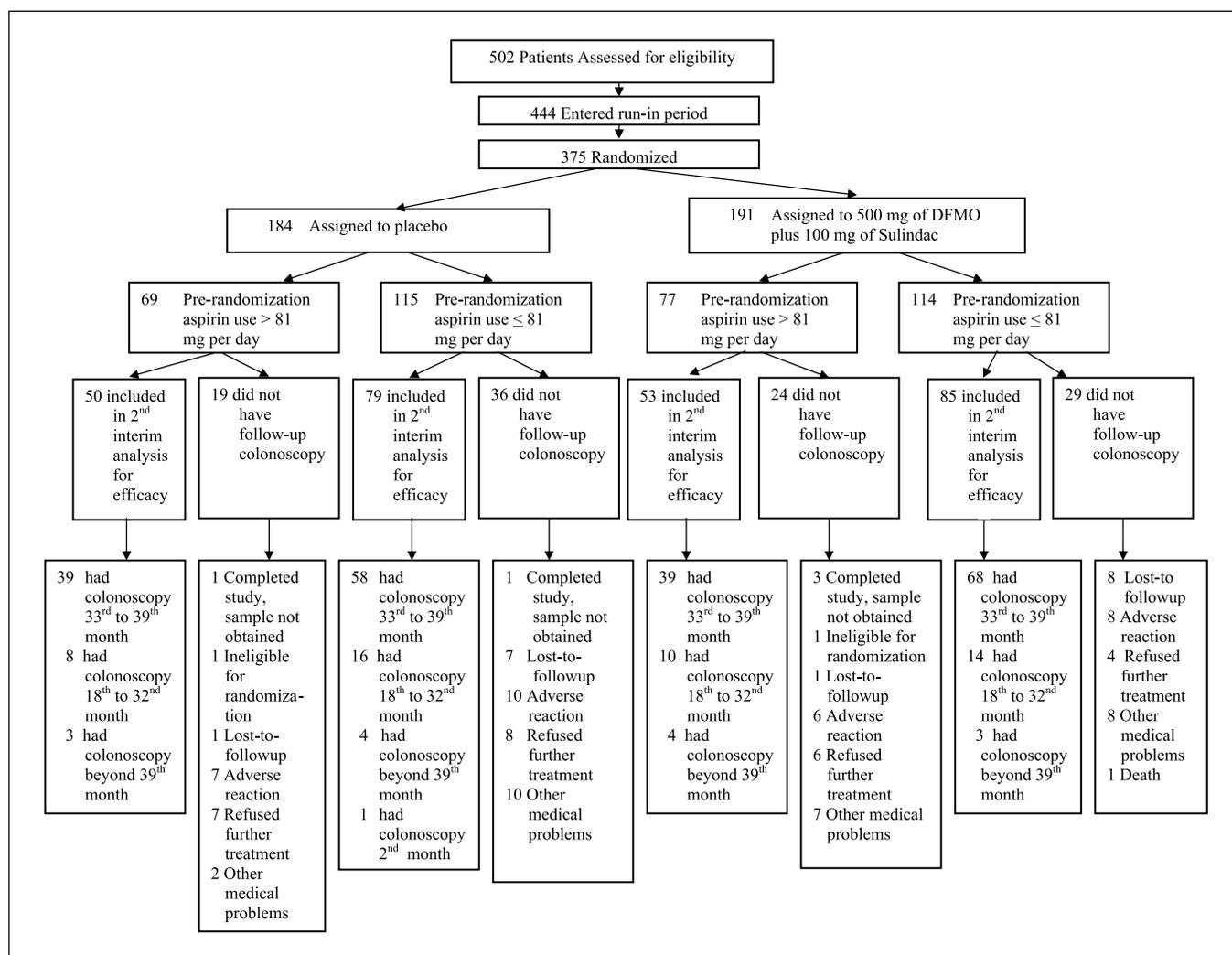


Fig. 1. Study schema.

Table 2. Risk of adenomas; evidence of substantial effect in active arm

	Follow-up colonoscopy 2 to 39 mo after beginning treatment (n = 267)		Follow-up colonoscopy 33 to 36 mo after beginning treatment (n = 204)	
	Placebo (n = 129)	DFMO/sulindac (n = 138)	Placebo (n = 97)	DFMO/sulindac (n = 107)
Detection of any adenoma				
Cumulative incidence of adenomas detected at end of the treatment (%)	53 (41.1)	17 (12.3)	42 (43.3)	12 (11.2)
Risk ratio* (95% CI)		0.30 (0.18-0.49)		0.26 (0.15-0.46)
P		<0.001		<0.001
Detection of advanced adenomas [†]				
Cumulative incidence of advanced adenomas detected at end of the treatment (%)	11 (8.5)	1 (0.7)	9 (9.3)	1 (0.9)
Risk ratio* (95% CI)		0.085 (0.011-0.65)		0.10 (0.013-0.78)
P		0.001		0.004
Detection of advanced adenomas with size ≥1 cm				
Cumulative incidence of advanced adenomas with size ≥1 cm detected at end of the treatment (%)	9 (7.0)	1 (0.7)	7 (7.2)	1 (0.9)
Risk ratio* (95% CI)		0.10 (0.013-0.81)		0.13 (0.016-1.03)
P		0.004		0.02
Detection of multiple adenomas (>1)				
Patients with >1 adenoma, incidence (%)	17 (13.2)	1 (0.7)	15 (15.5)	1 (0.9)
Risk ratio* (95% CI)		0.055 (0.0074-0.41)		0.060 (0.0081-0.45)
P		<0.001		<0.001
Sensitivity analysis imputing adenoma for patients without an end-point determination [‡]				
Cumulative incidence of adenomas detected at end of the treatment (%)	76/184 (41.3)	39/191 (20.4)		
Risk ratio* (95% CI)		0.49 (0.36-0.69)		
P		<0.001		

*Relative risk estimation by log-binomial regression. Likelihood ratio test *P* values are reported.

[†]Advanced adenomas in the placebo group included tubulovillous (3), intramucosal carcinoma (2), size ≥1 cm (6), and one serrated adenoma with high-grade dysplasia; the one advanced adenoma in the treatment group was an adenoma >1 cm.

[‡]Sensitivity analysis imputing adenoma for all patients without an end-of-study colonoscopy at the placebo rate of recurrence.

remaining patients as the prescribed efficacy end points had been met and because long-term follow-up of the remaining patients on trial was unlikely to change the conclusions about efficacy.

Based on power calculations, 292 subjects would provide maximal information for end point evaluation; the rate of colonoscopy was 91% (267 of 292) in this cohort and the final analysis was based on data from these 267 evaluable patients, comprising 71% of the randomized cohort. The primary analysis for efficacy measured adenomas at any time after randomization (Table 2). In the placebo group, 53 patients had at least one adenoma, compared with 17 patients in the treatment group. The estimated cumulative recurrence was 41.1% in the placebo group and 12.3% in the treatment group, corresponding to a risk ratio of 0.30 [95% confidence interval (95% CI), 0.18-0.49; *P* < 0.001] or a reduction of 70%. Accounting for the interim analyses, the bias-adjusted point estimate of the difference in polyp recurrence between the treatment and placebo groups was -0.2793 with a corrected 95% CI of -0.3933 to -0.1718. Aspirin (≤81 mg) use did not seem to affect the

number of total adenomas in either group. A sensitivity analysis in which adenomas were imputed at the observed placebo rate of recurrence for all patients without an end-of-study colonoscopy (Table 2) gave a risk ratio of 0.49 (95% CI, 0.36-0.69).

In the placebo group, 11 patients had advanced adenomas, whereas in the DFMO plus sulindac group only one advanced adenoma was detected. This corresponds to a risk ratio of 0.085 (0.011-0.65; *P* < 0.001) or a reduction of 92%. In the placebo group, 17 patients had more than one adenoma, compared with one patient randomized to active intervention, indicating a reduction of 95% (risk ratio, 0.055; 95% CI, 0.0074-0.41; *P* < 0.001). Similar results were obtained in a smaller group of patients who had colonoscopies between 36 and 39 months on treatment (Table 2).

Safety

Adverse events were carefully monitored throughout the study (Tables 3 and 4). At least one serious adverse event requiring an overnight hospitalization was reported in 31

Table 3. Incidence of adverse events after randomization categorized by COSTART

	Placebo (n = 184)	DFMO/ sulindac (n = 191)
Serious adverse events, no. patients with adverse event (%)*		
Adverse events requiring overnight hospitalizations	31 (16.9)	42 (22.0)
Risk ratio (95% CI)		1.31 (0.86-1.98)
P		0.21
All adverse events with a grade ≥ 3	15 (8.2)	21 (11.0)
Risk ratio (95% CI)		1.35 (0.72-2.53)
P		0.35
Deaths [†]	1 (0.5)	2 (1.1)
Risk ratio (95%)		NA
Any adverse event, no. patients with adverse events (%)		
All patients	153 (83.2)	171 (89.5)
Risk ratio (95% CI)		1.08 (1.00-1.17)
P		0.07
Cardiovascular (95% CI)	22 (12.0)	28 (14.7)
Risk ratio (95% CI)		1.23 (0.73-2.06)
P		0.44
Gastrointestinal events, no. patients (%)	14 (7.6)	24 (12.6)
Risk ratio (95% CI)		1.65 (0.88-3.09)
P		0.11
Audiometric evaluation, no. patients with adverse event / no. patients in cohort (%)*		
Self-reported hearing complaint reported as an adverse event	53 (28.8)	67 (35.1)
Risk ratio (95% CI)		1.22 (0.90-1.64)
P		0.19
Self-reported study-related hearing complaint reported as adverse event	30 (16.3)	36 (18.8)
Risk ratio (95% CI)		1.16 (0.74-1.80)
P		0.52

*Relative risk estimation by log-binomial regression. Likelihood ratio test *P* values are reported.

[†]Of the three deaths, one subject died during the trial due to traffic accident and the other subjects died 1 and 3 y, respectively, after study completion from causes judged by the investigator as unrelated to the intervention.

of 184 (16.9%) patients in the placebo group and in 42 of 191 (22.0%) patients in the DFMO plus sulindac group (risk ratio, 1.31; 95% CI, 0.86-1.98; *P* = 0.21). There was also no significant difference between the two arms in those patients experiencing a serious adverse event of grade ≥ 3 (Table 3). No drug-associated changes in serum levels of creatinine, alanine aminotransferase, or hemoglobin were measured. Reported renal, hypertensive, gastrointestinal, and cardiovascular disorders were analyzed separately, and no differences were detected between the two groups. Serious cardiovascular side effects (Table 4) occurred in 16 (8.4%) patients in the

treatment arm and in 9 (4.9%) patients in the placebo arm (risk ratio, 1.71; 95% CI, 0.78-3.78; *P* = 0.17).

There was no significant difference between groups in the proportions of patients with self-reported hearing loss (Table 3; risk ratio, 1.22; 95% CI, 0.90-1.64; *P* = 0.19), and in the normal speech range (500-3,000 Hz) no significant difference was noted between arms in the 259 tested participants (*P* = 0.17). For these models, after adjustment for age and gender, differences between groups remained nonsignificant (*P* = 0.19 and *P* = 0.15, respectively).

Of 262 participants who had air conduction audiograms at baseline and repeated audiograms from 18 to 36 months after beginning treatment, there were 25 of 136 (18.4%) in the DFMO plus sulindac group and 12 of 123 (9.8%) in the placebo group (*P* = 0.05) who experienced at least a 15-dB hearing reduction from baseline in ≥ 2 consecutive frequencies across the entire range tested (230-8,000 Hz; Table 4). Based on end-of-study audiograms, 30 patients had unilateral or bilateral hearing reductions of ≥ 15 dB from baseline in ≥ 2 consecutive frequencies across the entire range of frequencies tested. Of these, 12 had bilateral audiometric hearing reductions, 10 of 21 (48%) in the treatment arm and 2 of 9 (22%) in the placebo arm (*P* = 0.18). Follow-up audiograms obtained in these 12 patients showed that improvement occurred in 1 of 2 (50%) patients in the placebo arm and in 3 of 10 (30%) in the treatment group.

Discussion

The results from this randomized trial (Table 2) indicate that a low dose of the polyamine synthesis inhibitor DFMO plus the nonspecific nonsteroidal anti-inflammatory drug sulindac at a dose one half the usual therapeutic dose markedly reduced the recurrence of all adenomas (70% decrease), advanced adenomas (92% decrease), and recurrence of more than one adenoma (95% decrease) in a population of individuals at moderately high risk for sporadic adenomas (41% of patients receiving placebos developed recurrent adenomas). Although this study was not structured to determine whether colorectal cancer occurrence itself was affected, two participants in the placebo group, but none in the active treatment group, were diagnosed with colon cancer by the end of the study.

A major feature of this trial was the selection of a low dose of DFMO based on two sequential biomarker studies, the first 1 month in length and the second 12 months in length, in which a dose deescalation strategy was used (26-28). These studies allowed selection of the lowest dose of DFMO that produced a decrease in polyamine levels in the target of interest, colorectal mucosa. In the 12-month study, no evidence of a difference in toxicities between placebo and the low dose selected for the current trial was evident. Nevertheless, patients were carefully monitored for possible toxicities in the current trial.

At the time the current study was designed in 1997, there was no known concern about the cardiovascular toxicity of nonsteroidal anti-inflammatory drugs, including celecoxib and sulindac, with almost the entire focus on the decreased occurrence of gastrointestinal toxicity with cyclooxygenase-2 inhibitors (29, 30). At the time the current study was started (1999), selection of sulindac was based on its long-term prior broad use with an excellent clinical profile including

gastrointestinal toxicity in the low range for nonsteroidal anti-inflammatory drugs and evidence of activity in familial adenomatous polyposis (31). Although the clinical cardiovascular (and cerebrovascular) toxicity had not yet surfaced at that time, we were concerned with using a specific or selective cyclooxygenase-2 inhibitor based on mechanistic considerations (32). No statistically significant increase of gastrointestinal, hematologic, or cardiovascular or cerebrovascular toxicity was found

in our trial; however, the study was not designed to have adequate power to identify differences in toxicity rates between treatment groups.

Self-reported hearing changes were also not significantly different between the two groups. Although no evidence of a decrement in the normal speech range was documented, serial audiograms suggested a possible effect across a broader range of frequencies tested that was reversible in some cases.

Table 4. Detailed assessment of adverse events

	Placebo (n = 184)		DFMO/sulindac (n = 191)	
	Aspirin (n = 69)	Non-aspirin (n = 115)	Aspirin (n = 77)	Non-aspirin (n = 114)
<i>Cardiovascular</i>				
CAD, prior Hx*	0	1	3	0
CAD, new	0	1	1	0
MI, prior Hx	1	0	1	0
MI, new	0	0	3	1
CVA, prior Hx	0	0	0	0
CVA, new	0	1	1	1
CHF, prior Hx	1	0	1	0
Chest pain, new	0	4	0	4
Subtotal, prior Hx	2	1	5	0
Subtotal, new	0	6	5	6
Total		9 (4.9)		16 (8.4)
Risk ratio (95% CI) [†]		—		1.71 (0.78-3.78)
P		—		0.17
<i>Hearing</i>				
Audiometric evaluations at end of study, no. patients with adverse events / no. patients in cohort (%) [‡]				
Hearing loss at least 15 dB at ≥2 frequencies	24/123 (19.5)	35/136 (25.7)		
Risk ratio (95% CI) [†]		1.32 (0.83-2.09)		
P		0.23		
Hearing loss at least 15 dB at ≥2 consecutive frequencies	12/123 (9.8)	25/136 (18.4)		
Risk ratio (95% CI) [†]		1.88 (0.99-3.59)		
P		0.05		
Hearing loss at least 15 dB at ≥2 consecutive frequencies in the normal range (500-3,000 Hz)	7/123 (5.7)	14/136 (10.3)		
Risk ratio (95% CI) [†]		1.81 (0.75-4.33)		
P		0.17		
Bilateral audiometric changes at 36 mo or at least 6 mo off-study				
End of study, no. with bilateral changes (%) [§]	2/9 (22.2)	10/21 (47.6)		
Risk ratio (95% CI) [†]	—	2.14 (0.58-7.88)		
P	—	0.18		
At 6 mo posttreatment				
Improved	1/2 (50.0)	3/10 (30.0)		
Persistent	0/2 (0.0)	1/10 (10.0)		
Unilateral hearing loss with development of bilateral hearing loss	1/2 (50.0)	2/10 (20.0)		
Pending	0/2 (0.0)	4/10 (40.0)		

*Prior Hx, subjects had prior history.

[†]Relative risk estimation by log-binomial regression. Likelihood ratio test P values are reported.

[‡]All self-reported hearing complaints were recorded. Hearing thresholds were assessed for 259 patients with follow-up audiograms measured from 18 to 36 mo after beginning of therapy.

[§]Unilateral or bilateral change from baseline at 36 mo (n = 30; placebo, n = 9; DFMO/sulindac, n = 21).

^{||}Bilateral changes at 36 mo or at least 6 mo off-study (n = 12; placebo, n = 2; DFMO/sulindac, n = 10).

The complex details of the audiologic studies and analyses will be reported elsewhere.

The results in this randomized trial confirm the value of de-escalation studies before launching a full phase III trial in identifying a dose and regimen for the therapeutic prevention of adenomas that is both efficacious and with minimal toxicity. Larger and longer-term trials will be needed to determine the absolute risk of cardiovascular and cerebrovascular events and the clinical implications of audiologic changes from this regimen. Longer-term studies will also be needed to determine whether this combination regimen can reduce colorectal cancer incidence or improve/complement colorectal surveillance strategies in very high-risk individuals, in patients with low stage prior colorectal cancers, or in the post-adjuvant setting.

Disclosure of Potential Conflicts of Interest

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Difluoromethylornithine Plus Sulindac for the Prevention of Sporadic Colorectal Adenomas: A Randomized Placebo-Controlled, Double-Blind Trial

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