Curcumin Maintenance Therapy for Ulcerative Colitis: Randomized, Multicenter, Double-Blind, Placebo-Controlled Trial

HIROYUKI HANAI,[*,‡] TAKAYUKI IIDA,[‡] KEN TAKEUCHI,[‡] FUMITOSHI WATANABE,[§] YASUHIKO MARUYAMA,[§] AKIRA ANDOH,[‖] TOMOYUKI TSUJIKAWA,[‖] YOSIHIHIDE FUJIYAMA,[‖] KEIICHI MITSUYAMA,[¶] MICHIO SATA,[¶] MASAMI YAMADA,[#] YASUSHI IWAOKA,[#] KAZUNARI KANKE,[**] HIDEYUKI HIRAISHI,[**] KAZUHISA HIRAYAMA,[††] HAJIME ARAI,[‡‡] SHIGEHITO YOSHII,[‡‡] MASATO UCHIJIMA,[§§] TOSHI NAGATA,[§§] and YUKIO KOIDE[§§]

[*]Department of Endoscopic and Photodynamic Medicine and [§§]Department of Microbiology and Immunology, Hamamatsu University School of Medicine, Hamamatsu; [‡]Center for Gastroenterology, Hamamatsu South Hospital, Hamamatsu; [§]Department of Gastroenterology, Fujieda Municipal General Hospital, Shizuoka; [‖]Department of Internal Medicine, Shiga University of Medical Science, Shiga; [¶]Second Department of Medicine, Kurume University School of Medicine, Kurume; [#]Department of Gastroenterology, Hamamatsu Medical Center, Hamamatsu; [**]Department of Gastroenterology, Dokkyo University School of Medicine, Tochigi; [††]Department of Surgery, Hamamatsu Social Insurance Hospital, Hamamatsu; and [‡‡]Hamamatsu Mikatahara Seirei Hospital, Hamamatsu, Japan

Background & Aims: Curcumin is a biologically active phytochemical substance present in turmeric and has pharmacologic actions that might benefit patients with ulcerative colitis (UC). The aim in this trial was to assess the efficacy of curcumin as maintenance therapy in patients with quiescent ulcerative colitis (UC). **Methods:** Eighty-nine patients with quiescent UC were recruited for this randomized, double-blind, multicenter trial of curcumin in the prevention of relapse. Forty-five patients received curcumin, 1g after breakfast and 1g after the evening meal, plus sulfasalazine (SZ) or mesalamine, and 44 patients received placebo plus SZ or mesalamine for 6 months. Clinical activity index (CAI) and endoscopic index (EI) were determined at entry, every 2 months (CAI), at the conclusion of 6-month trial, and at the end of 6-month follow-up. **Results:** Seven patients were protocol violators. Of 43 patients who received curcumin, 2 relapsed during 6 months of therapy (4.65%), whereas 8 of 39 patients (20.51%) in the placebo group relapsed ($P = .040$). Recurrence rates evaluated on the basis of intention to treat showed significant difference between curcumin and placebo ($P = .049$). Furthermore, curcumin improved both CAI ($P = .038$) and EI ($P = .0001$), thus suppressing the morbidity associated with UC. A 6-month follow-up was done during which patients in both groups were on SZ or mesalamine. Eight additional patients in the curcumin group and 6 patients in the placebo group relapsed. **Conclusions:** Curcumin seems to be a promising and safe medication for maintaining remission in patients with quiescent UC. Further studies on curcumin should strengthen our findings.

Ulcerative colitis (UC) is a debilitating, chronic, relapsing-remitting IBD that afflicts millions of individuals throughout the world and produces symptoms that impair quality of life and ability to function.[1] Although factors like smoking cessation,[2] use of nonsteroidal anti-inflammatory drugs,[3] and stress[4] are known to provoke an exacerbation, clinical relapses are often unpredictable.

Currently, several drugs including sulfasalazine (SZ), mesalamine, corticosteroids, immunomodulators, and remicade are used to treat patients with active IBD.[5–12] However, these medications are associated with side effects that add to the disease complications when used either to induce remission or to prevent a recurrence.[9–15] Furthermore, given that the majority of patients with UC (approximately 70%) have a clinical course that is either relapsing-remitting or chronic continuous, there is a need for novel safe medications to maintain remission in patients with UC in whom the disease has reverted to a quiescent state.

Curcumin is a natural substance present in turmeric, the spice that gives food an exotic yellow color. Curcumin seems to have a broad spectrum of pharmacologic actions including antitumor, anti-inflammatory, and antioxidant effects.[16–20] The pleiotropic effects of curcumin are attributable in part to the inhibition of the transcriptional nuclear factor–κB (NF-κB).[21–23] In line with this background, recently we demonstrated that treatment with curcumin can prevent murine experimental colitis by inhibiting ÑF-κB activation and $CD4^+$ T-cell infiltration into the colonic mucosa.[24] This study aimed to assess the efficacy of curcumin as a maintenance therapy in patients with quiescent UC.

Patients and Methods

Patients

Between April 2004–July 2005, 8 centers in Japan enrolled a total of 89 patients. The study protocol was reviewed and approved by the Committees on Ethics of clinical trials involving human subjects at each institution, and the trial was conducted in accord with the Declaration of Helsinki. Inclusion criteria were (1) patient had a diagnosis of UC as confirmed by radiologic, endoscopic, or histologic criteria that are established by the Research Committee of Inflammatory Bowel Disease, the Japan Ministry of Health; (2) age between 13–65 years; (3) patient's UC had a clinical activity index (CAI) ≤4, stable for the previous 4 weeks; (4) patient had achieved remission with a corticosteroid ≥20 mg/day prednisolone or an alternative medication and had successfully ceased steroid therapy; and (5) patient had a hemoglobin of ≥10 g/dL. Exclusion criteria were (1) patient was receiving an immunomodulator like aza-

Abbreviations used in this paper: CAI, clinical activity index; EI, endoscopic index; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; NOS, nitric oxide synthase; SZ, sulfasalazine; TNBS, trinitrobenzene sulfonic acid; UC, ulcerative colitis.

1542-3565/06/$32.00
doi:10.1016/j.cgh.2006.08.008

thioprine, 6-mercaptopurine, or cyclosporine; (2) patients with severe cardiovascular diseases; (3) patients with laboratory abnormalities indicating anemia (hemoglobin <9 g/dL), leukopenia, thrombocytopenia, or abnormal coagulation; (4) patients with renal or liver disease, chronic pancreatitis, diabetes mellitus, or gallstone; (5) patients with infection, sepsis, or pneumonia; and (6) pregnant or nursing women. Dropout criteria were (1) patient exhibits complications during the study; (2) patient decides to withdraw from the trial at will; and (3) patient requires additional drug therapy that violates the inclusion criteria. Any adverse symptom was recorded in the diary kept by patients during the study. Laboratory investigations including a complete blood count and blood chemistry were performed 3 times, at baseline, at 3 months, and at the end of the treatment.

Methods

This study was to be a randomized, multicenter (8 hospital institutions), double-blind, and placebo-controlled clinical trial. Assignment to curcumin or placebo was according to a computer-generated randomization scheme done by the clinical pharmacist. Patients were given SZ (1.0–3.0 g/day; median, 2.0 g/day) or mesalamine (1.5–3.0 g/day; median, 2.25 g/day) plus 2 g curcumin, 1 g taken after breakfast and 1 g after the evening meal, or placebo for 6 months (Figure 1). Patients were then followed for an additional 6 months, during which either SZ or mesalamine was continued. All medications except SZ or mesalamine were discontinued 4 weeks before starting this study. All study personnel and participants were blinded to treatment assignment for the duration of the study. Only the study statisticians and the data monitoring committee could see unblinded data, but none had any contact with the study patients. Curcumin and placebo were made to have identical appearance (yellow), prepared by API Co, Ltd (Gifu, Japan). The compositions of curcumin and placebo are shown in Table 1.

Clinical Assessment

CAI was measured at entry (within 2 weeks before randomization), every 2 months, and then at the conclusion of the clinical trial, whereas endoscopic index (EI) was determined at entry and at the conclusion of the trial. Both CAI and EI were according to Rachmilewitz.[25] Patients who had a CAI ≤4 were considered to be in clinical remission, whereas relapse was defined as CAI ≥5.

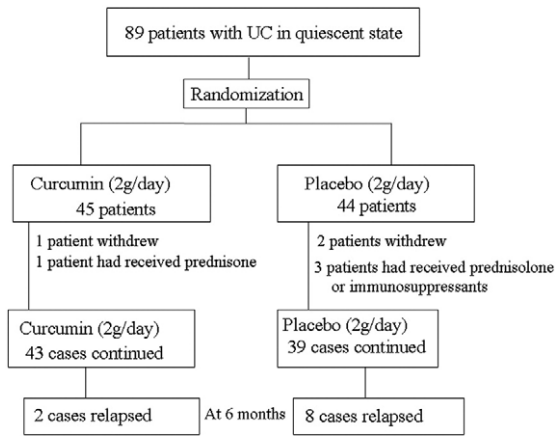

Figure 1. Summary of the study design, randomization, and clinical outcomes of the 6 months of treatment.

Table 1. Compositions of Medications (%)

Curcumin		Placebo	
Curcumin	50.0	Microcrystalline cellulose	25.0
Microcrystalline cellulose	42.5	Dextrin	29.6
Malitol	7.5	Cornstarch	10.0
		Malitol	35.0
		FD & C Yellow No. 5	0.15
		FD & C Yellow No. 6	0.04
		Caramel color	0.2
Total	100		100

Statistical Analysis

Data are presented as the mean ± standard deviation values and ranges unless indicated otherwise. For determining statistical significance, comparisons were made by using the Fisher exact test or the χ^2 test. P value <.05 was considered significant in all statistical evaluations.

Results

Clinical Outcomes

Seven patients (2 in the curcumin group and 5 in the placebo group) were excluded in line with patients' wishes. Hence, 43 patients in the curcumin group and 39 patients in the placebo group completed the study. Study groups were well-matched with respect to gender, age, duration of UC, recurrences during the past 2 years, clinical course, CAI, and EI (Table 2). Recurrent rates evaluated in all patients (intention to treat) also showed significant differences between the curcumin and the placebo groups (P = .049, Table 3). Relapses in the 2 groups during the 6-month study period together with the

Table 2. Demography of Patients at Baseline

Demography	Curcumin	Placebo	*P* value
Male/female	23/22	26/18	.52
Age, mean (*y*)	45.2 ± 15.8	39.7 ± 14.2	.11
Range	(18–75)	(21–68)	
Duration of UC (*mo*)	98.6 ± 74.2	93.5 ± 74.2	.77
Range	(11–305)	(5–336)	
No. of recurrences during past 2 y	1.6 ± 1.2	1.5 ± 1.0	.78
Range	(0–5)	(0–4)	
Clinical course (cases)			
First attack	5	4	
Relapsing-remitting	29	28	
Chronic continuous[a]	10	8	.89
CAI before study	1.3 ± 1.1	1.0 ± 1.1	.23
Range	(0–4)	(0–4)	
EI before study	1.3 ± 0.8	1.3 ± 1.0	.60
Range	(0–3.0)	(0–3.6)	

Mean ± standard deviation values and (ranges) are presented.
[a]Patients with chronic continuous UC had a CAI ≤4 for at least 4 weeks before entry. "Chronic continuous" is commonly used in Japan to indicate a CAI that oscillates between fully quiescent (0–1) and clinical remission (4) in some patients.

Table 3. Recurrence Rates at 6 and 12 Months Based on Intention to Treat

	Curcumin	Placebo	*P* value
No. of patients randomized	45	44	
No. of patients with recurrence at 6 mo	2	8	
% with recurrence at 6 mo	4.44	15.15	.049
95% confidence interval (%)	0.54–15.15	8.19–32.71	
No. of patients with recurrence at 12 mo	10	14	
% with recurrence at 12 mo	22.2	31.8	.433
95% confidence interval (%)	11.2–37.1	18.6–47.6	

Table 4. Recurrence Status at 6 Months

	Curcumin	Placebo	*P* value
No. of patients treated	43	39	
No. of patients with recurrence	2	8	
% with recurrence	4.65	20.51	.040
95% confidence interval	0.56–15.47	9.30–36.46	

Analysis is based on the number of eligible patients who completed the study, excluding the 7 patients who became protocol violators during the study.

follow-up data are presented in Figures 1 and 2. Of the 43 patients who received curcumin, 2 patients (4.55%) relapsed during 6 months, whereas 8 of 39 patients (20.51%) in the placebo group relapsed ($P = .040$) (Table 4).

We also determined the mean CAI and EI values before and after the treatment (Table 5). The mean CAI in the curcumin group was improved from 1.3 ± 1.1 at baseline to 1.0 ± 2.0 at 6 months ($P = .038$). In contrast, CAI in the placebo group showed significant deterioration; mean CAI increased from 1.0 ± 1.1 to 2.2 ± 2.3 ($P = .0003$). Furthermore, patients in the curcumin group had significantly improved EI, 1.3 ± 0.8 vs 0.8 ± 0.6 ($P = .0001$). The EI values in the placebo group showed no significant difference between baseline and post-treatment.

Follow-up Observations

A 6-month follow-up was done after the end of the 6-month study period. As shown in Figure 2, 8 additional patients in the curcumin group and 6 patients in the placebo group relapsed during the 6-month follow-up while being on SZ or mesalamine. There was no significant difference between the 2 groups with respect to relapse rates during the 6-month follow-up.

Safety Evaluation

A total of 9 mild and transient side effects in 7 of 89 patients were observed during curcumin maintenance therapy. Some patients experienced more than 1 event. The side effects included sensation of abdominal bulging, nausea, transient hypertension, transient increase in the number of stools, and elevated γ-guanosine triphosphate level. The elevated γ-guanosine triphosphate was observed in a patient who was a regular alcohol drinker. No patient discontinued curcumin therapy as a result of side effects, except 1 patient with hypertension.

Discussion

The clinical outcomes of this double-blind, placebo-controlled trial of curcumin therapy to sustain remission in patients with quiescent UC might be briefly summarized as follows: (1) 2 g/day curcumin in combination with SZ or mesalamine had significantly better clinical efficacy in the prevention of relapse compared with placebo plus SZ or mesalamine; (2) curcumin significantly improved both CAI and EI; and (3) curcumin was well-tolerated and was not associated with any serious side effect.

Most currently available conventional drugs used to treat UC are associated with unpleasant side effects. For example, nausea, vomiting, headaches, rash, fever, hepatitis, pancreatitis, nephritis, agranulocytosis, and male infertility are reported in approximately 30% of patients who take SZ.[1] The sulfa moiety of the drug is known to interfere with folic acid absorption. Even the mesalamine derivatives that lack the sulfa moiety are associated with fever, diarrhea, and abdominal discomfort. In contrast, none of these side effects were observed when patients were given curcumin. Curcumin is a diferulolymethane, a natural plant product extracted from the root of *Curcuma longa Linn*. It

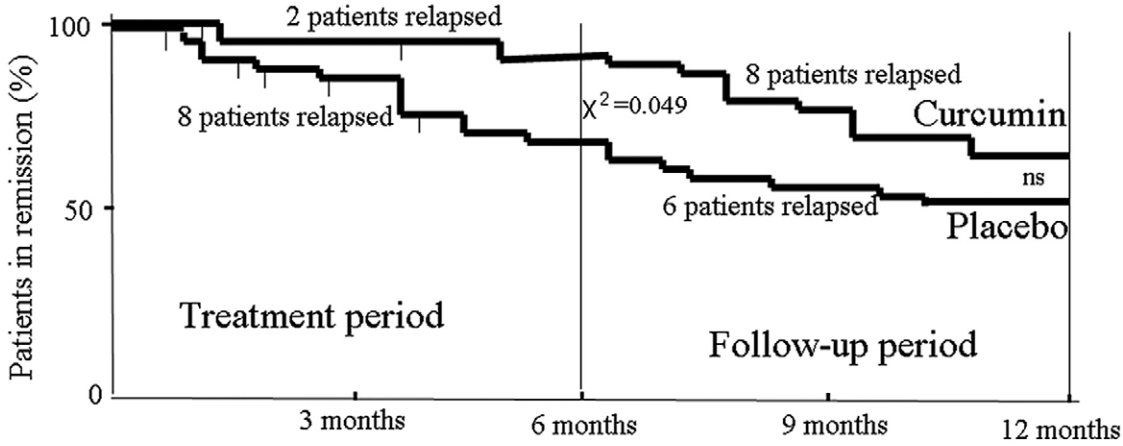

Figure 2. The Kaplan-Meier curves showing the efficacy outcomes during the 6 months of therapy and 6 months of follow-up.

Table 5. Changes in CAI and EI During the 6 Months of Treatment

	Curcumin		Placebo	
	Entry	6 Mo	Entry	6 Mo
CAI	1.3 ± 1.1	1.0 ± 2.0	1.0 ± 1.1	2.2 ± 2.3
P value	.038		.0003	
EI	1.3 ± 0.8	0.8 ± 0.6	1.3 ± 1.0	1.6 ± 1.6
P value	.0001		.0728	

P values by the χ^2 test.

is a common food additive popular for its pleasant mild aroma and exotic yellow color, not likely to cause side effects. In India and China, for centuries curcumin has been known as a medicinal plant. It is very likely that curcumin has several biochemical actions that are not yet elucidated. Recently, curcumin was reported to block the upstream of NF-κB and IκB kinase.[26] NF-κB is suspected to promote the expression of human IBD.[26–28] Consistent with this assertion, recently we demonstrated that curcumin can suppress colonic inflammation induced by trinitrobenzene sulfonic acid (TNBS) in a mice model of colitis.[24]

In the present study, only 2 of 43 patients treated with curcumin in combination with SZ or mesalamine relapsed during the 6 months of therapy, whereas 8 of 39 patients who received placebo with SZ or mesalamine relapsed during the same period. It is appropriate to mention that mesalamine alone when used as maintenance therapy during a 6-month period has an efficacy similar to that of SZ, which is equal to the placebo group in our study.[29,30] In addition, in this study, we added a 6-month follow-up to the 6-month treatment time during which patients received SZ or mesalamine only. Clinical assessment at the end of the follow-up showed no significant difference between the 2 groups. This supported our impression that curcumin, in fact, does suppress relapse.

The 2-g curcumin per day in this study is similar to the dose reported to have antitumor effect.[31] However, we admit that the dose of curcumin used in this study might not be the optimum and the most effective regimen. This could be viewed as one major limitation of our data. With this in mind, we believe that future studies in larger cohorts of patients should use multiple doses of curcumin, because a dose higher than 2 g/day might appear superior to 2 g/day.

Aminosalicylates have been reported to be inhibitors of NF-κB.[4] However, curcumin has broader effects on the NF-κB signal transduction pathways. In addition, curcumin inhibits mitogen-activated protein kinase (MAPK),[32] c-Fos, and nitric oxide synthase (NOS) activity,[33] thus potentially having a broader spectrum of anti-inflammatory effects compared with aminosalicylates (not to mention its safety).

In our study, both the clinical and endoscopic evaluation scores were significantly improved by curcumin therapy. Especially the endoscopic score was substantially improved compared with the placebo. Nine of the curcumin-treated patients reported some mild side effects such as abdominal bloating and nausea. Because the patients were also receiving SZ or mesalamine as well, we could not with certainty attribute these complaints to curcumin. A phase I human trial with 25 subjects using up to 8 g curcumin per day found no toxicity or serious side effects related to curcumin.[34] Therefore, we conclude that curcumin therapy is both effective and safe in maintaining UC remission.

In conclusion, the results of this study indicate that the turmeric component, curcumin, is potentially a promising medication for the treatment of IBD. In the near future, we plan to undertake a multiple-dose (including a high-dose) curcumin trial without an aminosalicylate as maintenance therapy in patients with quiescent UC.

References

1. Head KA, Jurenka JS. Inflammatory bowel disease part I: ulcerative colitis-pathophysiology and conventional and alternative treatment options. Altern Med Rev 2003;8:247–283.
2. Boyko EJ, Koepsell TD, Perera DR, et al. Risk of ulcerative colitis among former and current cigarette smokers. N Engl J Med 1987;316:707–710.
3. Rampton DS, Sladen GE. Relapse of ulcerative proctocolitis during treatment with non-steroidal anti-inflammatory drugs. Postgrad Med J 1981;57:297–299.
4. Kurina LM, Goldacre MJ, Yeates D, et al. Depression and anxiety in people with inflammatory bowel disease. J. Epidemiol Community Health 2001;55:716–720.
5. Wahl C, Liptay S, Adler G, et al. Sulfasalazine: a potent and specific inhibitor of nuclear factor kappa B. J Clin Invest 1998; 101:1163–1174.
6. Weber CK, Liptay S, Wirth T, et al. Suppression of NF-κB activity by sulfasalazine is mediated by direct inhibition of IκB kinase α and β. Gastroenterology 2000;119:1209–1218.
7. Bantel H, Berg C, Vieth M, et al. Mesalazine inhibits activation of transcription factor NF-κB in inflamed mucosa of patients with ulcerative colitis. Am J Gastroenterol 2000;95:3452–3457.
8. Xu C-T, Meng S-Y, Pan B-R. Drug therapy for ulcerative colitis. World J Gastroenterol 2004;10:2311–2317.
9. Allison MC, Dhillon AP, Lewis WG, et al, eds. Inflammatory bowel disease. London: Mosby, 1998:15–95.
10. Hanauer SB. Medical therapy of ulcerative colitis. Gastroenterology 2004;126:1582–1592.
11. Hanauer SB. Inflammatory bowel disease: epidemiology, pathogenesis, and therapeutic opportunities. Inflamm Bowel Dis 2006; 12:S3–S9.
12. Kornbluth A, Marion JF, Salomon P, et al. How effective is current medical therapy for severe ulcerative colitis? J Clin Gastroenterol 1995;20:280–284.
13. Taffet SL, Das KM. Sulphasalazine-adverse effects and desensitization. Dig Dis Sci 1983;28:833–842.
14. Present DH. How to do without steroids in inflammatory bowel disease. Inflamm Bowel Dis 2000;6:48–57.
15. Devos SA, Van Den Bossche N, De Vos M, et al. Adverse skin reactions to anti-TNF-alpha monoclonal antibody therapy. Dermatology 2003;206:388–390.
16. Jiang MC, Yang-Yen HF, Yen JJ, et al. Curcumin induces apoptosis in immortalized NIH 3T3 and malignant cancer cell lines. Nutr Cancer 1996;26:111–120.
17. Singh AK, Sidhu GS, Deepa T. Curcumin inhibits the proliferation and cell cycle progression of human umbilical vein endothelial cell. Cancer Lett 1996;107:109–115.
18. Huang TS, Lee SC, Lin JK. Suppression of c-Jun/AP-1 activation by an inhibitor of tumor promotion in mouse fibroblast cells. Proc Natl Avad Sci USA 1991;88:5292–5296.
19. Xu YX, Pindolia KR, Janakiraman N, et al. Curcumin, a compound with anti-inflammatory and anti-oxidant properties, down-regulates chemokine expression in bone marrow stromal cells. Exp Hematol 1997;25:413–422.
20. Joe B, Rao UJ, Lokesh BR. Presence of an acidic glycoprotein in

the serum of arthritic rats: modulation by capsaicin and curcumin. Mol Cell Biochem 1997;169:125–134.
21. Singh S, Aggarwal BB. Activation of transcription factor NF-κB is suppressed by curcumin (diferuloylmethane). J Biol Chem 1995; 270:2495–2500.
22. Kumar A, Dhawan S, Hardegen NJ, et al. Curcumin (diferuloylmethane) inhibition of tumor necrosis factor (TNF)-mediated adhesion of molecules and of nuclear factor-κB activation. Biochem Pharmacol 1998;55:775–783.
23. Jobin C, Bradham CA, Russo MP, et al. Curcumin blocks cytokine-mediated NF-κB activation and proinflammatory gene expression by inhibiting inhibitory factor I-κB kinase activity. J Immunol 1999; 163:3474–3483.
24. Sugimoto K, Hanai H, Tozawa K, et al. Curcumin ameliorates trinitrobenzene sulfonic acid (TNBS)-induced colitis in mice. Gastroenterology 2002;123:1912–1922.
25. Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomized trial. Br Med J 1989;298:82–86.
26. Schreiber S, Nikolaus S, Hamper J. Activation of nuclear factor κB inflammatory bowel disease. Gut 1998;42:477–484.
27. Neurath MF, Becker C, Barbulescu K. Role of NF-κB in immune and inflammatory responses in the gut. Gut 1998;43:856–860.
28. Rogler G, Brand K, Vogl D, et al. Nuclear factor κB is activated in macrophages and epithelial cells of inflamed intestinal mucosa. Gastroenterology 1998;115:357–369.
29. Lim W-C, Hanauer SB. Controversies with aminosalicylates in inflammatory bowel disease. Rev Gastroenterol Disord 2004;4: 104–117.
30. McIntyre PB, Rodrigues CA, Lennard-Jones JE, et al. Balsalazide in the maintenance treatment of patients with ulcerative colitis: a double-blind comparison with sulphasalazine. Aliment Pharmacol Ther 1988;2:237–243.
31. Cheng A-L, Hsu C-H, Lin J-K, et al. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high risk or pre-malignant lesions. Anticancer Res 2001;21:2895–2900.
32. Squires MS, Hudson EA, Howells L, et al. Relevance of mitogen activated protein kinase (MAPK) and phosphotidylinositol-3-kinase/proteinkinase B (PI3K/PKB) pathways to induction of apoptosis by curcumin in breast cells. Bichem Pharmacol 2003; 65:361–376.
33. Chan MM, Huang Hi, Fenton MR, et al. In vivo inhibition of nitric oxide synthase gene expression by curcumin, a cancer preventive natural product with anti-inflammatory properties. Biochem Pharmacol 1998;55:1955–1962.
34. Chainani-Wu N. Safety and anti-inflammatory activity of curcumin: a component of turmeric (Curcuma longa). J Altern Complement Med 2003;9:161–168.

Address requests for reprints to: Yukio Koide, MD, PhD, Department of Microbiology and Immunology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Hamamatsu 431-3192, Japan. e-mail: koidelb@hama-med.ac.jp; fax: 81-53-435-2335.

Supported by the Broad Medical Research Program (IBD-0069) from The Eli and Edythe L. Broad Foundation.