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# Tolerability of Curcumin in Pediatric Inflammatory Bowel Disease: A forced dose titration study

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## Background

Inflammatory bowel disease (IBD) is characterized by chronic intestinal inflammation in the absence of a recognized etiology. Human and animal studies support the theory that patients with IBD have dysfunction of reactive and innate immune systems in response to an unknown trigger. Therapy of IBD with anti-inflammatory or immunosuppressive agents is effective, but carries many well-known adverse effects and intolerabilities.[1]

Curcumin is the principal natural curcuminoid (a class of phenols) found in the plant *Curcuma longa* which is used as a food additive known as tumeric. In India, it has been used as a spice and food preservative as well as for treatment in Ayurveda (traditional Indian medicine). In the United States it is also commonly used as a coloring agent in foods. Curcumin has a broad spectrum of pharmacologic actions, including anti-inflammatory, anti-oxidant and anti-tumor effects.[2] Many in vitro and animal studies have been conducted to evaluate curcumin's effect on inflammation. The pleiotropic effects of curcumin are attributable in part to the inhibition of the transcriptional nuclear factor-kappa B (NF-kappa B) with subsequent inhibition of tumor necrosis factor, IL-12 and IL-2; all important cytokines in the inflammatory cascade.[2–5] Recent animal and adult human studies have shown beneficial effects in intestinal inflammation. Given its anti-inflammatory effects and its prior usage in Ayurvedic medicine, we conducted a tolerability study to assess increasing dosages of curcumin in children with IBD.

## Method

The protocol was approved by the Seattle Children's Hospital Institutional Review Board. Patients were recruited from the outpatient service of the Division of Pediatric Gastroenterology at University of Washington, Seattle Children's Hospital. Informed consent was obtained from all parents, and assent was obtained from all participants.

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Prospectively patients with Crohn's or ulcerative colitis in remission or with mild disease (Pediatric Crohn's Disease Activity Index (PCDAI) < 30 or Pediatric ulcerative colitis activity index (PUCAI) score <34) were enrolled in a tolerability study (ClinicalTrials.gov Identifier NCT00889161 & IND 103,826).[6,7] Curcumin was supplied as 500 mg capsules (Vital Nutrients Inc, Middletown, CT, USA). The curcumin extract underwent both drug quality testing for curcuminoid content and food testing at an independent lab prior to dispensing (Integrated Biomolecule Corporation, Tucson, Az, USA). All patients received curcumin in addition to their standard therapy. No placebos were used in this study. Patients initially received 500mg twice a day for 3 weeks. Using the forced dose titration design, doses were increased to 1 gram twice daily at week 3 for a total of three weeks and then titrated again to 2 grams twice daily at week 6 for three weeks. Patients were seen at baseline, and at three, six and nine weeks. Validated measures of disease activity, using the PUCAI or PCDAI, were completed during each study visit. The Monitoring of Side Effect System (MOSES) scale was obtained at Week 3, Week 6 and Week 9. Patients were given the option of discontinuation or de-escalation of curcumin dose to the previously tolerated dose if toxicity was detected. Laboratory measures were obtained at each visit including complete blood count, sedimentation rate, C-reactive protein, creatinine, amylase, and Alanine transaminase (ALT).

## Results

Eleven patients (7 male/4 female; 14.6 ± 2.3 years, range 11–18 years) enrolled in the study. (Table 1). Six had Crohn's disease and five had UC. Six patients were on mesalamine and five patients were on an anti-TNF biologic therapy. Prior to beginning the study, all patients were on maintenance medication for greater than 6 months except two patients with ulcerative colitis and mild active disease who had been on maintenance medication for 2 months. Nine patients completed the study. Two patients dropped from the study for reasons unrelated to the study drug i.e. unable to make clinic follow-up. All other patients tolerated curcumin well at all study doses. Two patients reported increase gassiness during three visits. Inconsistent reports of symptoms (symptoms occurring only once or resolving on their own occurred in the majority of patients but were not felt to be related to the curcumin by patient, parent or physician. All symptoms reported were mild, not clearly related to curcumin and did not require de-escalation of the curcumin. Laboratory studies remained within normal range during the study. Three patients had lowering of PUCAI or PCDAI scores. Two patients with ulcerative colitis had PUCAI scores decrease 20 points indicating remission (scores dropped from 30 to 10 and 25 to 5, respectively). The Crohn's patients score dropped from 5 to 0 suggesting improvement. No participants experienced a relapse or worsening of symptoms while on the study medication.

## Discussion

Curcumin is a natural compound found in the plant *Curcuma longa* which is used as a food additive known as tumeric.[8] Humans appear to tolerate curcumin well. In India, the average intake of tumeric in the diet is approximately 2–2.5 grams per day in a 60 kg individual. This corresponds to an intake of 60–100 mg of curcumin daily.[9] Humans appear to be able to tolerate high doses of curcumin without significant side-effect. In a prospective phase-I study in adults using up to 8 grams per day of curcumin, no toxic effect of curcumin was found.[10] Studies evaluating curcumin in patients with rheumatoid arthritis, post surgical inflammation, and uveitis have shown beneficial effects without side effect.[11,12]

A pilot study in adults with ulcerative proctitis or Crohn's disease showed a reduction in symptoms with administration of 550 mg curcumin three times a day.[16] Curcumin has also been used in adults with ulcerative colitis in a randomized double-blind trial in the

prevention of relapse.[17] In this study, patients received standard treatment (sulfasalazine/mesalamine) with either placebo or curcumin. Using doses of 1 gram twice a day over a 6 month period, patients receiving curcumin showed a significant decrease in relapse (4.6% vs. 20.5% p=0.04). Recurrence rates evaluated on the basis of intention to treat showed significant difference between curcumin and placebo (p=0.049). Furthermore, curcumin improved both clinical activity index (p=0.038) and endoscopic index (p=0.0001), thus suppressing the morbidity associated with UC.

Currently, 36–50% of pediatric patients treated for IBD in gastroenterology clinics have used complementary and alternative therapies[18,19]. In most instances there are limited data on efficacy, tolerability and side-effects of these interventions. This is the first study to prospectively assess the tolerability of curcumin in pediatric inflammatory bowel disease. Our results show that in this small sample of pediatric patients curcumin is tolerated at doses up to 2 grams twice a day. This pilot study suggests that curcumin may be used as an adjunctive therapy for individuals seeking a combination of conventional and alternative medicine without clinically significant side effects or adverse events. Further studies are required to fully assess the safety and efficacy of curcumin in larger studies of patients with pediatric inflammatory bowel disease.

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**Table 1**

Patient Characteristics

| | Sex / age | Diagnosis | Baseline/9 week PUCAI or PCDAI | Lab changes during study* | Concomitant Medications | Finished study |
|---|---|---|---|---|---|---|
| 1 | 14 yo Male | UC | 0 / 0 | None | Anti-TNF antibody therapy | Yes |
| 2 | 14 yo Female | Crohn's disease | 0 / 0 | None | Anti-TNF antibody therapy | Yes |
| 3 | 14 yo Male | Crohn's disease | 0 / 0 | None | Anti-TNF antibody therapy & mesalamine | Yes |
| 4 | 17 yo Male | Crohn's disease | 0 / 0 | None | Anti-TNF antibody therapy | Yes |
| 5 | 11 yo Female | UC | 30 / 0 | None | Mesalamine therapy | Yes |
| 6 | 13 yo Female | UC | 25 | None | Mesalamine therapy | No |
| 7 | 18 yo Female | Crohn's disease | 0 / 0 | None | Anti-TNF antibody therapy | Yes |
| 8 | 15 yo Male | Crohn's disease | 0 / 0 | None | Mesalamine therapy | Yes |
| 9 | 12 yo Male | UC | 0 | None | Anti-TNF antibody therapy | No |
| 10 | 18 yo Male | Crohn's disease | 5 / 0 | None | Mesalamine therapy | Yes |
| 11 | 15 yo Male | UC | 25 / 5 | None | Mesalamine therapy | Yes |

*Labs evaluated include CBC, C-reactive protein, albumin, amylase, ALT, and creatinine.