

Trichuris suis Therapy for Active Ulcerative Colitis: A Randomized Controlled Trial

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See editorial on page 1117.

Background & Aims: Ulcerative colitis is most common in Western industrialized countries. Inflammatory bowel disease is uncommon in developing countries where helminths are frequent. People with helminths have an altered immunological response to antigens. In animal models, helminths prevent or improve colitis by the induction of regulatory T cells and modulatory cytokines. This study determined the efficacy and safety of the helminth *Trichuris suis* in therapy of ulcerative colitis. **Methods:** This was a randomized, double blind, placebo-controlled trial conducted at the University of Iowa and select private practices. *Trichuris suis* ova were obtained from the US Department of Agriculture. The trial included 54 patients with active colitis, defined by an Ulcerative Colitis Disease Activity Index of ≥ 4 . Patients were recruited from physician participants and were randomly assigned to receive placebo or ova treatment. Patients received 2500 *Trichuris suis* ova or placebo orally at 2-week intervals for 12 weeks. **Results:** The primary efficacy variable was improvement of the Disease Activity Index to ≥ 4 . After 12 weeks of therapy, improvement according to the intent-to-treat principle occurred in 13 of 30 patients (43.3%) with ova treatment compared with 4 of 24 patients (16.7%) given placebo ($P = .04$). Improvement was also found with the Simple Index that was significant by week 6. The difference in the proportion of patients who achieved an Ulcerative Colitis Disease Activity Index of 0–1 was not significant. Treatment induced no side effects. **Conclusions:** Ova therapy seems safe and effective in patients with active colitis.

The development of ulcerative colitis seems to involve both genetic and environmental factors. Current theories suggest that ulcerative colitis results from an aberrant immune response to normal luminal flora initiated by unknown causes. Inflammatory bowel disease

(IBD) is common in industrialized countries and rare in developing regions of the world. The reason for this difference is not known, but the high rate of helminth colonization in less developed countries could be a protective factor.¹ Helminths could be beneficial because of their unique capacity to decrease hyperreactive immune responses.^{2,3} In support of this premise, helminth eggs^{1,4,5} and live intestinal worms (unpublished data, David E. Elliot, 2004) have been shown to protect mice from colonic inflammation in experimental murine IBD and to even reduce ongoing disease activity. Also, patients with ulcerative colitis and Crohn's disease showed clinical improvement without adverse effects after treatment with live *Trichuris suis* ova in an open trial.⁶ Because of these epidemiological, experimental, and clinical observations, this double blind, placebo-controlled clinical trial was initiated to evaluate the efficacy and safety of *T suis* therapy in ulcerative colitis.

Materials and Methods

Participant Selection

Subjects were selected from patients with active ulcerative colitis seen in the University of Iowa's Center for Digestive Diseases and select gastroenterology practices in the State of Iowa. Patients 18 to 72 years old were eligible to enroll if they had active colitis involving at least the rectosigmoid colon. Standard criteria were used to establish the diagnosis, and activity was assessed by using the Ulcerative Colitis Disease Activity Index (UCDAI).⁷ The index assesses 4 variables: stool frequency, severity of bleeding, mucosal appearance, and the physician's overall assessment of the disease activity. Each variable is scored from 0 to 3, so the total index score ranges from 0 to 12. Because the UCDAI requires performing a flexible sigmoidoscopy, a secondary index was used to describe the course of the patients every 2

Abbreviations used in this paper: IL, interleukin; Th, T helper; UCDAI, Ulcerative Colitis Disease Activity Index.

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weeks. This was the Simple Clinical Colitis Activity Index (Simple Index), designed and validated by Walmsley et al,⁸ which is based on 5 clinical criteria (day and night stool frequency, urgency of defecation, blood in the stool, general well-being, and extracolonic features).

The following medications were allowed and continued at the same dose throughout the study: (1) oral sulfasalazine, mesalamine, or mesalamine derivative, if receiving it for >8 weeks and if receiving the same dose for at least 4 weeks; (2) oral prednisone up to 25 mg/day, if receiving it for >8 weeks and if receiving the same dose for at least 4 weeks; and (3) azathioprine or 6-mercaptopurine if receiving it for >6 months and if receiving the same dose for at least 8 weeks. Patients needed a hemoglobin level of >10.0 g/dL, a white blood count between 5000 and 15,000/ μ L, a platelet count >150,000/ μ L, no iron or vitamin B₁₂ deficiency, total bilirubin <1.5 mg/dL, aspartate aminotransferase and alanine aminotransferase <100 U/dL, alkaline phosphatase <250 U/dL, blood urea nitrogen <40 mg/dL, and serum creatinine <2.0 mg/dL. Women needed a negative pregnancy test and needed to practice birth control.

Patients were excluded if their UCDAI was <4. They also were excluded if there was fulminant colitis, an anticipated need for blood transfusion for gastrointestinal bleeding, or peritonitis. Patients were not enrolled if (1) stools contained enteric pathogens or *Clostridium difficile* toxin; (2) treatment in the last 12 weeks included cyclosporine, methotrexate, or immunomodulatory agents other than azathioprine/6-mercaptopurine; (3) treatment in the last 2 weeks included antibiotic, antifungal, or antiparasitic medications; (4) they had active hepatitis B, hepatitis C, cytomegalovirus, herpes simplex, or human immunodeficiency virus; (5) there was a history of cancer; (6) other clinically significant diseases were present that could interfere with protocol compliance or interpretation of the results; or (7) there was chemical abuse.

Study Agent Preparation and Interventions

Trichuris suis worms were isolated from the colons of specific pathogen-free pigs. The worms were cultured in vitro to allow ova production. Ova were placed into phosphate-buffered saline (PBS) containing penicillin/streptomycin/amphotericin B at 22°C for 5–6 weeks to allow embryonation. Ova were then treated with 0.2% K₂Cr₂O₇ to render them bacteria free and were washed with sterile saline. The ova were stored at 5°C in PBS. Samples of ova were cultured for viral and bacterial pathogens by using standard methods to ensure that they were free of pathogens. Viability and infectivity of stored ova were tested at intervals by inoculation of pigs. Ova remained viable for at least 9 months.

All patients received and ingested their placebo or *T suis* doses at the University of Iowa. The ova were counted by enumerating the number of eggs in an aliquot of solution by using a microscope and Sedgewick–Rafter counting chamber. Aliquots containing 2500 ova were added to vials containing PBS to make a total volume of 0.8 mL with charcoal (375 μ g/mL). Placebo vials contained 0.8 mL of PBS

with charcoal (375 μ g/mL) to ensure that the contents were masked. The placebo and active treatment vials were indistinguishable. This dose of *T suis* ova was the same as that used in our previous open-label pilot study.⁶ Neither mixture had taste or caused symptoms. An individual not involved in the study and who had no patient contact prepared and coded all vials. This individual, an experienced nurse investigator, assigned participants to receive ova or placebo by using a set of random numbers that was selected at the time of enrollment. No blocking or stratification schemes were used. A set of 6 charcoal masked vials containing ova or vehicle was prepared for each participant as he or she was enrolled. These 6 vials were given to the coordinator of this study, who was blinded to the treatment group throughout the study. When contents were ready for administration at each biweekly visit, the study coordinator diluted the vial contents with a commercial drink and gave the contents to the subject for oral consumption.

Study Design

The University of Iowa Institutional Review Board approved the study. All subjects gave informed consent, were willing participants, and were able to complete follow-up assessments. The specific objectives were to determine the efficacy and safety of *T suis* ova therapy in patients with active ulcerative colitis in comparison with those treated with placebo. The following were obtained at entry, 6 weeks, and 12 weeks: medical history and physical examination, pregnancy test, complete blood count, erythrocyte sedimentation rate, C-reactive protein, liver profile, stool examination for ova and parasites, bacterial pathogens, and *C difficile* toxin. Flexible sigmoidoscopy was performed at weeks 0 and 12 to assess mucosal inflammation.

The subjects returned every 2 weeks, and the study coordinator gave them the coded ova or placebo suspension. Patients kept diaries describing their clinical symptoms as required to calculate the UCDAI and Simple Index. The patients were asked about side effects and changes in their condition. The study remained double-blinded until all subjects completed the project. Entry IBD medications were not changed during the course of the study.

Outcome Measures and Statistical Analysis

Statistical analyses were performed according to the principles of intention to treat and per protocol. The analyses for intention to treat were based on all randomized patients. The clinical improvement at 12 weeks, defined as a decrease in the UCDAI ≥ 4 , was the primary measure of efficacy. Clinical remission, as defined by UCDAI of ≤ 2 , was a secondary end point. The primary efficacy measure was compared between the ova and placebo group by using the 2-sided Fisher exact test. To test for changes in the Simple Index over the course of treatment, the linear mixed model analysis for repeated measures was used. Pairwise comparison of each follow-up week from baseline was performed with Dunnett's test.

The baseline characteristics of the 2 study groups were compared, including sex, age, weight, disease activity, dura-

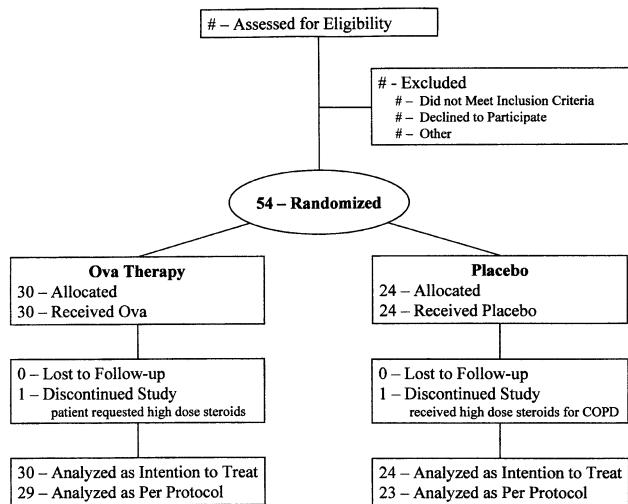


Figure 1. Flow diagram of study participants. COPD, chronic obstructive pulmonary disease.

tion of disease, duration of exacerbation, anatomic site of involvement, use of 5-aminosalicylates, corticosteroids, azathioprine or 6-mercaptopurine, hemoglobin, leukocyte and platelet count, and current smoking status. Chi-square tests were used to compare the distributions of categorical variables. Two-sample *t* tests were used for continuous variables if the appropriate normality assumptions were valid. Otherwise, the Wilcoxon rank-sum test was used. Plus-minus values are SE.

The decision to select approximately 27 patients per treatment group was based on the assumption that 20% of the placebo-treated group would improve by week 12 by using a decrease in UCDAI ≥ 4 as the primary outcome measure of improvement. It was projected that the statistical test at the .05 significance level would be able to detect a difference of at least 40% in the overall response rates between the placebo and ova treatment groups with 80% power.

Results

Study Patients

A total of 54 patients were enrolled between March 2001 and March 2003, and 52 completed the 12-week study (Figure 1). Of the 54 enrollees, 24 were treated with placebo, and 30 received helminthic ova. There were no significant differences between the ova- and placebo-treated groups in any of the baseline demographic, hematologic, biochemical, or disease characteristics (Table 1). Most patients had had their disease for many years (8.1 ± 0.9 years) and were dealing with lengthy exacerbations (11.6 ± 1.5 months) refractory to therapy before enrollment.

Compliance with the study protocol was excellent. All patients returned on schedule for their evaluations and therapy and completed their diaries, and no patient was lost to follow-up. Two patients were withdrawn because

of protocol violations. A placebo-treated subject received parenteral hydrocortisone followed by high-dose oral prednisone for chronic obstructive pulmonary disease 1 week after randomization. A patient treated with ova received high-dose corticosteroids given at week 4 because he did not wish to continue.

Clinical Efficacy

The results were similar whether the data were analyzed according to the intention-to-treat or per-protocol principle. With the intention-to-treat principle, a favorable response (decrease in UCDAI ≥ 4) occurred in 13 of 30 (43.3%) subjects treated with ova and 4 of 24 (16.7%) placebo-treated subjects ($P = .04$). Per protocol, the response rate was 13 of 29 (44.8%) for ova therapy and 4 of 23 (17.4%) for placebo ($P = .04$; Figure 2).

The mean initial UCDAI for all patients was 8.7 ± 0.3 . For the 13 patients who responded to ova, the initial UCDAI was 8.8 ± 0.4 , thus indicating that their disease activity was similar in severity to that of the group as a whole. The mean UCDAI of the responders at 12 weeks was 2.8 ± 0.4 . The number of patients who achieved UCDAI of 0–1 was 1 of 24 for placebo and 3 of 30 for *T suis*. This was not statistically significant (Figure 3).

Table 1. Baseline Characteristics of Patients Treated With Placebo or Ova^a

Variable	Placebo (n = 24)	Ova (n = 30)
Sex, male/female (% male)	14/10 (58%)	18/12 (60%)
Age (y)	39.7 ± 2.6	38.0 ± 2.2
Weight (kg)	83.6 ± 3.9	82.7 ± 4.2
UCDAI	8.7 ± 0.5	8.8 ± 0.4
Duration of disease (y)	8.7 ± 1.3	7.7 ± 1.3
Duration of present exacerbation (mo)	10.1 ± 1.7	12.7 ± 2.5
Site of disease		
Left side	10/24 (42%)	18/30 (60%)
Pancolitis	14/24 (58%)	12/30 (40%)
Medications at entry		
No medications	4/24 (17%)	5/30 (17%)
Mesalamine alone	6/24 (25%)	11/30 (37%)
Corticosteroid alone	3/24 (13%)	1/30 (3%)
Azathioprine alone	1/24 (4%)	0/30 (0%)
Mesalamine + corticosteroid	5/24 (21%)	7/30 (23%)
Mesalamine + azathioprine/6-MP	3/24 (13%)	3/30 (10%)
Corticosteroid + azathioprine/6-MP	2/24 (8%)	0/30 (0%)
Mesalamine + corticosteroid + azathioprine/6-MP	0/24 (0%)	3/30 (10%)
Hemoglobin (g/dL)	13.1 ± 0.06	13.9 ± 0.26
White blood cell count (cells $\times 1000/\mu\text{L}$)	8.8 ± 0.73	8.5 ± 0.65
Platelet count (cells $\times 1000/\mu\text{L}$)	361 ± 36	346 ± 16
Smoking status (current smokers/total)	0/24	2/30

6-MP, 6-mercaptopurine.

^aPlus-minus values are SE. None of the differences between groups was significant.

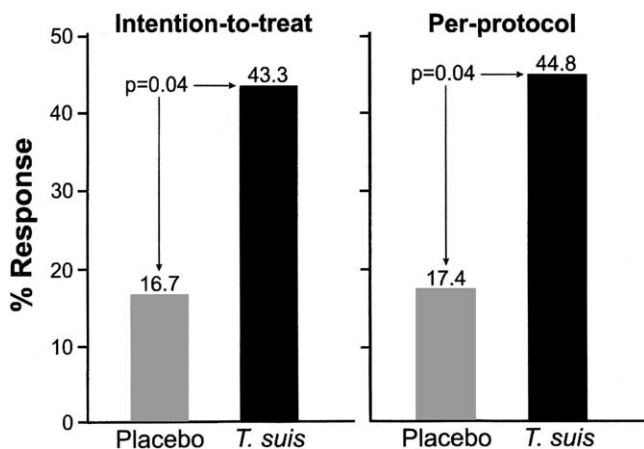


Figure 2. Percentage of patients achieving response. Response was defined as a decrease in UCDAI of ≥ 4 at week 12. Values for the intention-to-treat analysis are based on all 54 patients enrolled, whereas those for the per-protocol analysis are based on 52 patients. One patient withdrew from each of the placebo- and ova-treatment groups.

Post hoc exploratory analyses of clinically relevant end points were performed by using the 4 components of the UCDAI (frequency of diarrhea, blood in stool, mucosal appearance, and overall assessment of clinical response). With the intention-to-treat analysis, ova-treated patients had significant improvements in stool frequency ($P = .0011$), blood in the stool ($P = .0413$), mucosal appearance ($P = .00008$), and overall assessment ($P = .0011$) compared with their baseline values (Figure 4). The mean UCDAI went from 8.77 ± 0.35 to 6.1 ± 0.61 ($P = .0004$) over the 12-week study. The placebo-treated subjects showed significant improvement only in stool frequency ($P = .0488$). Their mean UCDAI went from 8.75 ± 0.46 to 7.5 ± 0.66 ($P = .1167$).

A secondary analysis was conducted by using the Simple Index to describe the clinical course every 2 weeks of placebo- vs. ova-treated patients (Figure 5). At weeks 8 and 12, the comparison between placebo- and ova-treated patients was statistically different ($P = .0226$ and $.0310$, respectively), and there was a trend toward significance at week 10 ($P = .0736$). Compared with time 0 baseline, the Simple Index of ova-treated patients was different at weeks 6 through 12, but placebo-treated patients showed no such change.

The response of patients to ova was analyzed according to site of disease, duration of disease, length of current exacerbation, and type of ongoing drug therapy. Seven of the 13 (54%) responders had total colonic involvement, whereas the ova-nonresponder group had total colonic involvement in 29% ($P = .18$). The mean duration of disease for the responders was 7.8 ± 2.2 years, and that of the nonresponders was 7.6 ± 1.6 years. The mean

duration of the current exacerbation for the responders was 7.3 ± 1.6 months, and that for the ova-nonresponders was 16.9 ± 3.9 months ($P = .05$). Patients continued on their pre-enrollment ulcerative colitis medications throughout the trial (eg, azathioprine, 6-mercaptopurine, mesalamine, and up to 25 mg of prednisone). Use of these medications did not seem to influence responsiveness to *T suis* ova, although the subgroups were too small for statistical comparison.

Safety Results

There were no side effects or complications attributable to the therapeutic agent. The following adverse or unexpected events occurred during the study and were reported to our institutional review board. In the placebo-treated group, 1 patient developed pneumonia and an exacerbation of chronic obstructive pulmonary disease that required antibiotic and corticosteroid therapy. A second patient had pain due to rib fracture. A third placebo-treated patient developed hyperglycemia that prompted treatment with an oral agent. Only 1 patient in the ova-treated group experienced an adverse event. This was mild hydrochlorothiazide-induced pancreatitis that resolved after the drug was stopped.

There were no significant differences between groups in any of the baseline hematologic or routine biochemical parameters. No individuals in either group developed significant changes in their hematologic, hepatic, or renal profile during the 12-week study period. No worms or ova were identified in stools.

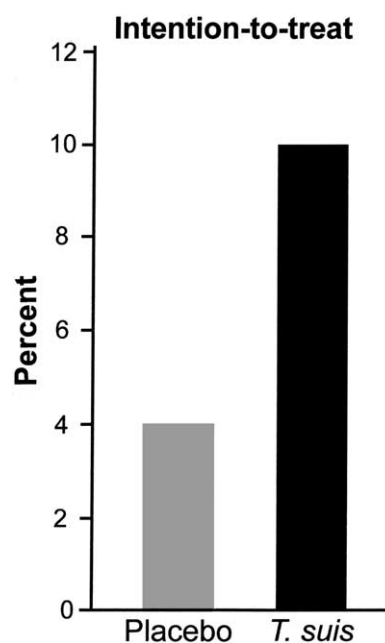


Figure 3. Percentage of patients achieving UCDAI 0–1 (not significant).

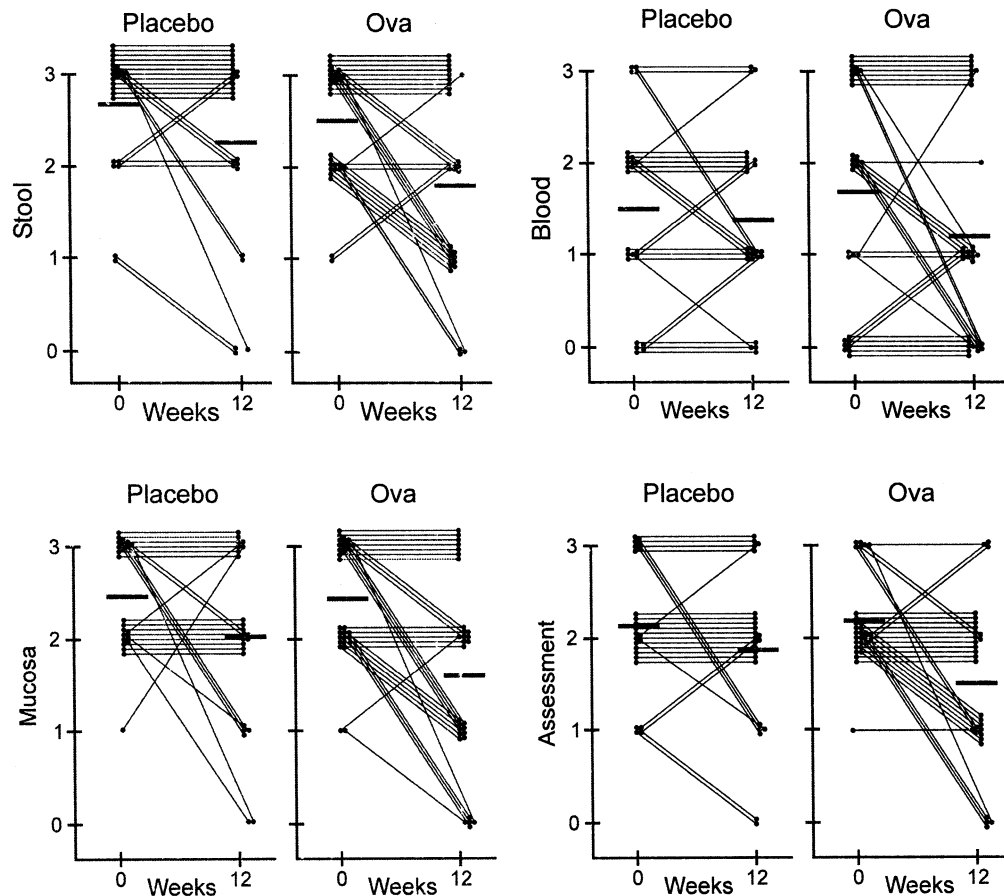


Figure 4. UCDAI scores for stool frequency, stool blood, mucosal appearance, or overall assessment at baseline and week 12. Ova-treated subjects had significant mean improvements in all parameters. Placebo-treated subjects showed improvement only in stool frequency. Analysis was intention to treat.

Discussion

This double-blind study suggests that helminth ova therapy administered every other week induces improvement in patients with active ulcerative colitis. Statistically significant differences between placebo- and ova-treated patients at 12 weeks were shown by 2 separate indices and were supported by post hoc analyses. Patients with a decrease in the UCDAI of ≥ 4 seemed to have clinically significant improvement.

There were few remissions, however, as defined by UCDAI ≤ 2 . Many subjects had lengthy, severely active, and resistant disease. Many of these patients had previously experienced treatment failure with conventional medical therapy. The placebo remission rate was low in comparison to that of other trials,⁹ and this may reflect the chronic and refractory nature of the disease under treatment. It remains to be determined whether broader subject selection or different dosing schedules of the agent will induce more remissions.

Subset analysis was limited because of the small sample size; however, there was a suggestion that patients

with total colonic involvement and shorter durations of disease activity were more likely to respond to ova therapy. The Simple Index data suggest that the therapeutic response to the agent occurs in approximately 6 weeks. The study was appropriately blinded, because charcoal added to the ova and placebo vials effectively obscured the nearly-microscopic ova.

No organisms or ova were identified in stools. Stools were examined for ova 2 weeks after each dose of *T suis* ova (just before the next dose). Thus, ova administered orally would not be evident in the stool 2 weeks later. Although eggs can hatch and develop into worms in the human host, the worms normally do not mature to egg-producing adults for approximately 2 months. This may explain why ova were not seen in the stools.

Trichuris suis induced no symptoms or signs different from placebo and caused no apparent complications, even though half of the patients treated with ova were receiving corticosteroids, azathioprine/6-mercaptopurine, or both. We have given approximately 2000 doses of *T suis* ova to approximately 100 IBD patients over several years with-

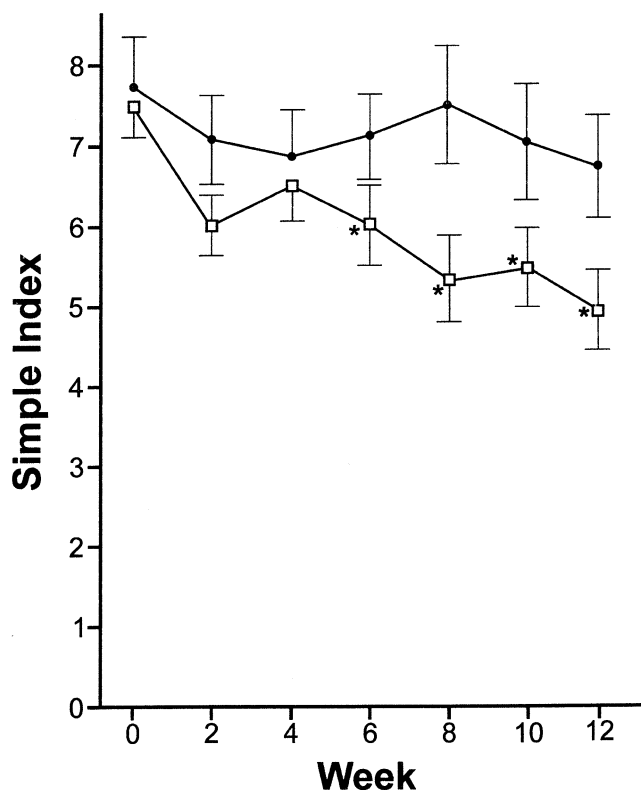


Figure 5. Simple Index for placebo-treated (●) and ova-treated patients (□). Compared with baseline (time 0), there was a progressive decrease in the Simple Index in the ova-treated patients. * $P = .032$ at week 6; $P = .003$ at week 8; $P = .014$ at week 10; $P < .0001$ at week 12. There was no significant change over time in the Simple Index in the placebo group.

out any apparent side effects or complications (unpublished data). Although there is limited clinical experience, it seems that this biological agent may be safe.

Helminths such as *T suis* are parasitic animals. *Trichuris suis* is the porcine whipworm. Humans are not a natural host for *T suis*, and no diseases are associated with exposure to this agent. However, *T suis* can colonize humans temporarily under experimental conditions.¹⁰ *Trichuris trichiura*, the human whipworm, is closely related to *T suis*.¹¹ This could explain why *T suis* can colonize humans briefly. *Trichuris ova* mature in the soil and are ingested by the host to initiate colonization. The ova hatch in the duodenum without invading the host. The larvae mature into adult worms in 6–8 weeks, localizing to the terminal ileum and colon. In the natural host, they live from 1 to 2 years. Mature worms produce ova that exit the host with the stool, but ova are not infective until they incubate in the soil for several weeks; this prevents direct host-to-host transmission.

Ulcerative colitis is a chronic inflammatory disease of the colon that causes diarrhea, bleeding, and abdominal pain. The leading theory is that it results from an inap-

propriate immune response to contents of the intestinal lumen. Regulatory T cells and modulatory inflammatory mediators such as interleukin (IL)-10, transforming growth factor β , and prostaglandin E_2 help limit immune responses and tissue injury at intestinal mucosal surfaces. Animal models of IBD suggest that these factors help protect from IBD.^{12–14}

This study did not address mechanisms of action. We speculate that *T suis* improves ongoing IBD through the induction of immunomodulatory circuitry. There are complex interactions between helminths and their hosts. People with helminths have dampened immune reactivity to unrelated concurrent antigenic exposures.^{2,3} Mice bearing helminths have blunted T-helper type 1 (Th1) responses.^{15–18} The host develops a Th2 response to helminths associated with the production of IL-4 and IL-13, and this impedes the development of Th1 cells. Excessive Th1 responsiveness is an important pathogenic factor in the development of IBD in many animal models.¹⁹ However, ulcerative colitis is sometimes considered more of a Th2 than a Th1 response. Paradoxically, epidemiological studies show that helminths probably prevent the development of asthma (a Th2 disease).²⁰ Thus, the response to a helminth may impede inappropriate Th2 responses to other substances as well. Helminths induce regulatory T cells and promote the production of powerful immunomodulatory molecules such as IL-10, transforming growth factor β , and prostaglandin E_2 , and this could underlie their broad protective effects^{4,21} (unpublished data).

The prevalence of IBD is not uniform worldwide.^{22–28} Although numerous hypotheses have been advanced to explain these differences, no epidemiological cause has been established. One possible explanation for the differences described previously could be the state of helminth colonization. Currently, more than one third of the world's population has helminths, and worm infestation is most common in children. In the United States and other developed countries, helminth infection has steadily declined except in recent immigrants from less developed countries²⁹ and in indigenous populations living in underserved regions.³⁰ Helminths regulate their host's immune system. Thus, modern-day lack of exposure to helminths because of hygienic practices may be an important factor that contributes to the risk for IBD.

In conclusion, *T suis* is a unique therapy for ulcerative colitis. Its ease of use affords additional advantages. *Trichuris suis* probably will have a high safety profile. In Iowa, approximately 20% of pig herds harbor this organism, but there are no illnesses attributable to occupational *T suis* exposure. It is possible that optimal dosing and timing of administration may increase effi-

cacy. Other helminths or chemical components from these organisms may have equal or greater efficacy. These and other unresolved issues require additional larger clinical trials to refine the therapeutic role of intestinal helminths in ulcerative colitis.

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Sippy of the Sippy Diet Regimen



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Bertram Welton Sippy (1866–1924) was born in the village of Neptune in Richland County, Wisconsin. After 2 years at the University of Wisconsin he transferred to Rush Medical College in Chicago where he was awarded his MD degree in 1890. He took a job as a railroad surgeon in Montana in order to obtain funds for an 18-month tour of hospitals and clinics in Europe, including a stint with the famed Professor Carl Ewald in Berlin. On his return to Chicago he set up a practice of internal medicine, with an emphasis on neurology but without neglect of the broader field. He quickly acquired a reputation as an astute diagnostician and superb teacher. It is said his showmanship held his students spellbound and doubtlessly contributed to his success with patients. An ardent believer in Schwartz' dictum ("No acid, no ulcer"), he promoted for the treatment of acute peptic ulcer disease a strict regimen of hourly milk and cream feedings supplemented by frequent, large doses of antacids and often by periodic gastric aspiration. A generation of physicians found this a highly effective means of hastening the healing of peptic ulcers. Unfortunately, the Sippy regimen did little to prevent ulcer recurrence, and Sippy's program was later superseded by more efficacious therapy.

—Contributed by WILLIAM S. HAUBRICH, M.D.

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