

# *Trichuris suis* Seems to Be Safe and Possibly Effective in the Treatment of Inflammatory Bowel Disease

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**OBJECTIVES:** Inflammatory bowel disease (IBD), especially Crohn's disease (CD), probably results from failure to downregulate a chronic Th1 intestinal inflammatory process. Induction of a Th2 immune response by intestinal helminths diminishes Th1 responsiveness. This study evaluates the safety and effectiveness of helminthic ova in the treatment of active IBD.

**METHODS:** We studied four patients with active CD and three with ulcerative colitis (UC). In an initial treatment and observation period, a single dose of 2500 live *Trichuris suis* eggs was given orally, and patients were followed every 2 wk for 12 wk. Baseline medications were continued at the same dose throughout the study. Safety was monitored by following the patients' clinical status and laboratory studies at regular intervals. Patients also were monitored regularly using the Crohn's Disease Activity Index, Simple Clinical Colitis Activity Index (SCCAI), and the Inflammatory Bowel Disease Quality of Life Index (IBDQ). To assess safety and efficacy with repetitive doses, two patients with CD and two with UC were given 2500 ova at 3-wk intervals as maintenance treatment using the same evaluation parameters.

**RESULTS:** During the treatment and observation period, all patients improved clinically without any adverse clinical events or laboratory abnormalities. Three of the four patients with CD entered remission according to the Crohn's Disease Activity Index; the fourth patient experienced a clinical response (reduction of 151) but did not achieve remission. Patients with UC experienced a reduction of the Clinical Colitis Activity Index to 57% of baseline. According to the IBD Quality of Life Index, six of seven patients (86%) achieved remission. The benefit derived from the initial dose was temporary. In the maintenance period, multiple doses again caused no adverse effects and sustained clinical improvement in all patients treated every 3 wk for >28 wk.

**CONCLUSIONS:** This open trial demonstrates that it is safe to administer eggs from the porcine whipworm, *Trichuris suis*, to patients with CD and UC. It also demonstrates improvement in the common clinical indices used to describe disease activity. The benefit was temporary in some patients with a single dose, but it could be prolonged with maintenance therapy every 3 wk. The study suggests that it is possible to downregulate aberrant intestinal inflammation in humans with helminths. (Am J Gastroenterol 2003;98:2034–2041. © 2003 by Am. Coll. of Gastroenterology)

## INTRODUCTION

Inflammatory bowel disease (IBD) likely results from dysregulated immune responses to intestinal contents. As the immune system responds to foreign substances, inflammatory cells secrete and respond to regulatory cytokines. Two counter-regulatory patterns of cytokine secretion (Th1, Th2) can be identified in many immune responses. The Th1 response typically occurring in viral and bacterial infections is characterized by an increase in interleukins (IL)-12 and interferon- $\gamma$ , and Th2 by increased IL-4, IL-5, and IL-13. Polarized Th1 responses impede expression of Th2 cytokines and polarized Th2 responses impede Th1 activity. Inflammatory bowel disease, especially Crohn's disease (CD), is an overly active and destructive Th1 inflammatory response, possibly induced by intestinal bacteria (1, 2). The cytokine profile in active ulcerative colitis (UC) shows significant interferon- $\gamma$  release but is not as polarized as that seen in CD (1). It is currently accepted that UC is not clearly a Th1-dominated disease. The proinflammatory cytokines IL-1 $\beta$ , IL-6, IL-8, and tumor necrosis factor- $\alpha$  increase in both active UC and CD.

Intestinal helminths induce Th2 cytokine release and non-specifically downregulate Th1 responsiveness (3–5). Epidemiological studies show that IBD is most common in Western industrialized countries that are characterized by affluent societies living in sanitized environments. Alternatively, IBD is rare in developing countries with less clean environ-

ments and more crowded living conditions. The explanation for this difference in prevalence has always been speculative, but it should be noted that the prevalence of IBD is inversely proportional to the prevalence of helminthic parasites in that population. It has been estimated that more than 1 billion individuals harbor intestinal nematodes worldwide (6). Persons carrying helminths are more apt to mount a diminished Th1 response when challenged with other antigens (4, 5). This may prevent an overly active Th1 inflammatory response at mucosal surfaces such as occurs in CD. Genetically susceptible persons who are never exposed to helminths might lack a strong counteractive Th2 immune response, and these individuals may develop a poorly regulated and destructive intestinal Th1 response resulting in chronic colitis or ileitis.

Under experimental conditions, a number of helminths have been shown to induce Th2-type inflammation and also to downmodulate the Th1 immune responses to unrelated bacterial and viral infections (7–9). Therefore, colonization with intestinal helminths might be beneficial in reducing inflammation in patients with IBD.

The possibility that intestinal helminths might protect their host from developing or maintaining active IBD caused us to consider the use of one of these agents as treatment. The ideal biological agent should colonize the intestine without invading the host, causing symptoms, or creating illness. The source of the organism should be pathogen-free to minimize the potential of cotransmitting other diseases such as HIV, hepatitis B, C, or E, and it should not be a public health hazard to cohabitants or other close associates. The porcine whipworm *Trichuris suis* fulfills these criteria.

The life cycle of *T. suis* begins with the ingestion of embryonated eggs. *T. suis* eggs must incubate in the soil for a minimum of 4–6 wk to embryonate. Embryonated eggs hatch in the proximal small bowel. The larvae migrate aborally and attach to the mucosa of the distal small bowel and proximal colon. After several weeks, they mature and begin to shed eggs. In the porcine host, ordinary colonization produces little intestinal injury, but heavy colonization may induce inflammation, blood loss, and abdominal pain. *T. suis* may be carried in the porcine intestine for months and years, but they can not proliferate to increase parasite load. It has been established that *T. suis* and *T. trichiura* are distinct organisms (10, 11). *T. suis* is not a human parasite, but the ova are capable of colonizing a human host for several weeks and then are eliminated from the body without any specific therapy. In a study by Beer (11), *T. suis* eggs were administered to human volunteers without adverse effect. Eggs that are shed in the stool are not capable of colonizing another host because they are not yet embryonated. Therefore, we chose to harvest worms from pigs and collect their excreted eggs for use in this study. This method has the great advantage of reducing the risk to a potential human host and the approach poses no public health hazard.



**Figure 1.** The photomicrograph shows a *Trichuris suis* ovum containing a viable parasite larva. The egg is from the lot we used in this study, and it is about 90  $\mu\text{m}$  in greatest diameter.

The purpose of the study was to determine whether ova from the porcine helminth *T. suis* could be safely administered to patients with active UC and CD and to observe what effect it might have on indices of disease activity and quality of life.

## MATERIALS AND METHODS

### Treatment With *T. suis*

Adult worms were harvested from the intestinal mucosa of colonized pathogen-free pigs, washed in sterile buffers, incubated in antibiotics, and then cultured in sterile tissue culture medium in the presence of antibiotics (12). The eggs deposited by cultured worms were isolated, washed, and placed in 0.2% potassium dichromate solution at 22°C for 5–6 wk with aeration to obtain infective first-stage larvae (Fig. 1). Eggs were washed twice in sterile water and resuspended in the desired amount of saline based on a calculated dose of 2500. Before the study started, the infectivity of the eggs was checked by recovery of adult worms in pigs inoculated with known numbers of eggs. Approximately 10–20% of the estimated infective eggs developed into adult worms.

Each egg preparation was rigorously tested to confirm absence of bacterial and viral pathogens such as *Shigella*, *Salmonella*, *Campylobacter*, *Yersinia*, enterotoxigenic *Escherichia coli*, cytomegalovirus, herpes simplex virus, adenovirus, and enteroviruses using standard microbiological techniques.

The absence of swine hepatitis E viral genome in the *T. suis* eggs was confirmed by a negative reverse transcription polymerase chain reaction (RT-PCR). Total RNA was extracted from 100 ml of medium containing *T. suis* eggs using RNA STAT-50LS reagent (Tel-Test, Friendswood, TX) as described by the manufacturer (13). Reverse transcription was performed for 1 h at 37°C using 200 units of MMLV reverse transcriptase in the presence of random hexamers as primers (13). This PCR generates product of 199 bp detected by 2% agarose gel electrophoresis. Positive control was a swine hepatitis E virus isolate with 98% homology with US-1 human hepatitis E virus in the nested PCR target region (Y.V. Karetnyi and S.J. Naides, GenBank accession number AF097722).

The eggs were stored in aliquots of 1 ml of water containing 2500 ova at 4°C until they were administered to the

study subjects. The eggs remained viable and were able to colonize pigs even after 1 yr of storage.

### Study Protocol

The University of Iowa Institutional Review Board approved the study protocol. In total, we studied seven patients with refractory IBD (four with CD and three with UC). After baseline studies were performed, selection criteria were met (as outlined below), and informed consent was obtained, we gave 2500 live *T. suis* eggs orally with 30 ml of Gatorade (Gatorade, Chicago, IL). Patients were followed every 2 wk without additional helminth ova therapy for  $\geq 12$  wk. Baseline medications were continued at the same dose throughout the period. Safety was monitored by following the patients' clinical status and laboratory studies at regular intervals (see Assessment of Safety). The baseline and follow-up efficacy responses were monitored every 2 wk using standard clinical indices (see Measurement of Disease Activity). This treatment and observation period was continued for at least 12 wk. The numerical results at baseline and at 2, 4, 6, 8, and 12 wk were compared in tables and graphs.

After the first five patients were treated, no adverse events were encountered and all patients seemed to improve. Because the response was temporary in some patients, we requested and received permission to give repetitive doses. We wanted to explore whether multiple doses were safe and whether the benefit could be extended. After a treatment and observation period of at least 12 wk, two patients with CD and two with UC were given additional doses of 2500 ova at 3-wk intervals in a maintenance period. Again, no changes in baseline medications were made. Safety and efficacy were monitored at 3-wk intervals using the same parameters.

### Patient Selection Criteria

Patients aged  $>18$  yr were eligible for inclusion if they had active symptomatic UC manifested by bleeding or diarrhea, active inflammation on flexible sigmoidoscopy, or active Crohn's colitis on colonoscopy and a Crohn's Disease Activity Index (CDAI)  $>180$ . Women of childbearing potential were required to have a negative  $\beta$ -human chorionic gonadotropin ( $\beta$ -HCG) test and to agree to stay on birth control pills for the duration of the study. Patients were hematologically and biochemically stable for 2 months. They continued on their medications at the same dosage throughout the study. If they were on prednisone, antibiotics, or a 5-aminosalicylate drug, the dose had to have been stable for  $>2$  months. If they were on azathioprine or 6-mercaptopurine, the dose had to have been stable for  $>4$  months. They were also required to understand the protocol and agree to follow it, sign the informed consent document, and return every 2 wk for reassessment and administration of the study drink.

Patients were excluded if they had fulminant colitis or a CDAI  $<220$ , an ileostomy or colostomy, an extensive resection of bowel  $>100$  cm, or if the need for surgery was

imminent or anticipated. Particular attention was made to exclude patients with symptoms of impending obstruction. Patients were excluded if they had had cancer of any type, a history of alcohol or drug abuse, stools positive for pathogens, ova, or parasites, *Clostridium difficile* (*C. difficile*) toxin, or a significant and concurrent systemic infection such as hepatitis B virus, hepatitis C virus, or HIV. They were also excluded if they had other severe or progressive systemic diseases or if they were unwilling or unable to adhere to the protocol. After a thorough discussion of the rationale for the study and full disclosure of the risks and benefits, they gave written informed consent to participate.

### Assessment of Safety

All patients underwent an initial history and physical examination and a flexible sigmoidoscopy or colonoscopy to determine their baseline status and to be certain that they had active disease. The following baseline studies were obtained before egg ingestion: complete blood count, hepatic enzymes and bilirubin, erythrocyte sedimentation rate and C-reactive protein, urinalysis,  $\beta$ -HCG (for women of childbearing potential), stool for culture, ova and parasite examination, and *C. difficile* toxin assay. To detect any problems or complications as a result of the treatment, the physical assessment and above studies were repeated at regular 2-wk intervals (the urinalysis,  $\beta$ -HCG, stool culture, and *C. difficile* toxin assay were not monitored during the study).

### Measurement of Disease Activity

The primary criteria for determining the effect of the therapy included the Inflammatory Bowel Disease Quality of Life questionnaire (IBDQ) (14), the Crohn's Disease Activity Index (CDAI) (15), or the Simple Clinical Colitis Activity Index (SCCAI) (16). The IBDQ is now used to assess broadly the impact of therapy in nearly all IBD therapeutic trials. Patients filled out the questionnaire at every visit throughout the study.

The patients kept a daily diary for the elements of the CDAI and SCCAI every week throughout the study. The CDAI is widely accepted as the measure of effect in numerous studies of therapeutic agents in Crohn's disease. Although it has limitations, the CDAI allows ready comparisons among studies. The SCCAI, designed and validated by Warmlesley and Ayres (16), was chosen to describe the degree of illness in the patients with UC. The index is based on the following five clinical criteria: day and night stool frequency, urgency of defecation, blood in the stool, general well being and extracolonic features. Its correlation with the more comprehensive Powell-Tuck index (17) is highly significant ( $r = 0.959$ ). Its correlation with the laboratory-based Complex Integrated Disease Activity Index of Seo *et al.* (18) is also highly significant ( $r = 0.924$ ). Current studies commonly define remission as a drop in the CDAI to  $<150$  points and a rise in the IBDQ score to  $>170$  points.

**Table 1.** Initial Patient Characteristics and Treatment

Patient Number	Age (yr)	Disease Location	Duration (yr)	Prior Ileal Resection	Prior Medication	5-ASA (g/day)	Prednisone (mg/day)	6-MP/AZA (mg/kg/day)
<b>CD</b>								
1	39	Left colon	8	No	AZA*, HDP*	0	15	0
2	32	TI/colon	10	No	AZA*, HDP*	2.4	0	2.0
3	49	NTI/colon	10	Yes	AZA**, HDP*	3.0	0	0
4	60	NTI/colon	17	Yes	AZA*, HDP*	3.2	10	0
<b>UC</b>								
5	35	Sigmoid	10	No	HDP*	3.2	0	0
6	32	Left colon	10	No	6-MP**, HDP*	6.4	20	0
7	65	pancolitis	5	No	HDP*	2.4	10	2.5

HDP = high-dose prednisone (>40 mg); 6-MP/AZA = azathioprine \* no benefit, \*\* pancreatitis; NTI = neoterminal ileum; TI = terminal ileum.

We use these definitions and add the definition of remission in UC as an SCCAI of  $\leq 4$  points.

## RESULTS

Seven patients met the selection criteria and were included in the study; four of these patients had CD and three had UC. All were evaluated and managed throughout the trial at the University of Iowa Hospitals and Clinics. Initial clinical characteristics of the patients are shown in Table 1. All patients had had their disease  $\geq 5$  yr and they had all been treated with high dose prednisone ( $\geq 40$  mg), 6-mercaptopurine/azathioprine, or both during the preceding year without benefit. The exceptions were two patients who could not be treated with 6-mercaptopurine or azathioprine because of prior pancreatitis associated with these drugs. These three medications were being taken at the beginning of the trial and continued throughout the entire study at the same dose.

### Safety

In the initial treatment and observation period, no patient experienced any adverse effects that could be attributed to the study agent. No clinically significant changes in the blood count or hepatic tests occurred in any subject at any time during the study. No recognizable adverse clinical effects occurred in any of the subjects. After the initial

treatment and observation period, four patients (patients 3, 4, 6, and 7) were treated repetitively with multiple doses at 3-wk intervals for  $\geq 30$  wk (maintenance period). These four patients experienced no detectable adverse physical effects from ingestion of multiple doses of ova during the observation period of  $\geq 28$  wk, and there were no clinically significant changes in any of the monitored laboratory studies. Patient 1 had a prolonged remission and did not require additional therapy for 7 months when he moved to another state. Patients 2 and 5 were unreliable in their follow-up and not considered for long-term maintenance.

### Clinical Results During the Initial Treatment and Observation Period

Patients were treated with a single dose of 2500 eggs and then observed. The baseline and biweekly IBDQ scores are shown in Table 2. An index of  $\geq 170$  is generally considered to indicate remission; using this criterion, six of seven patients (86%) had achieved remission at 8.3 wk. The mean IBDQ progressively rose from a mean of 130 at entry to a high of 169 at wk 8 or 130% of baseline (Table 2). The mean length of remission, considering only the six patients who attained it, was 8 wk. The time course of remission for patients with CD and UC is shown in Figure 2. The percentage of patients in remission at 2-wk intervals is dependent on the clinical index used to define it. There is a lag

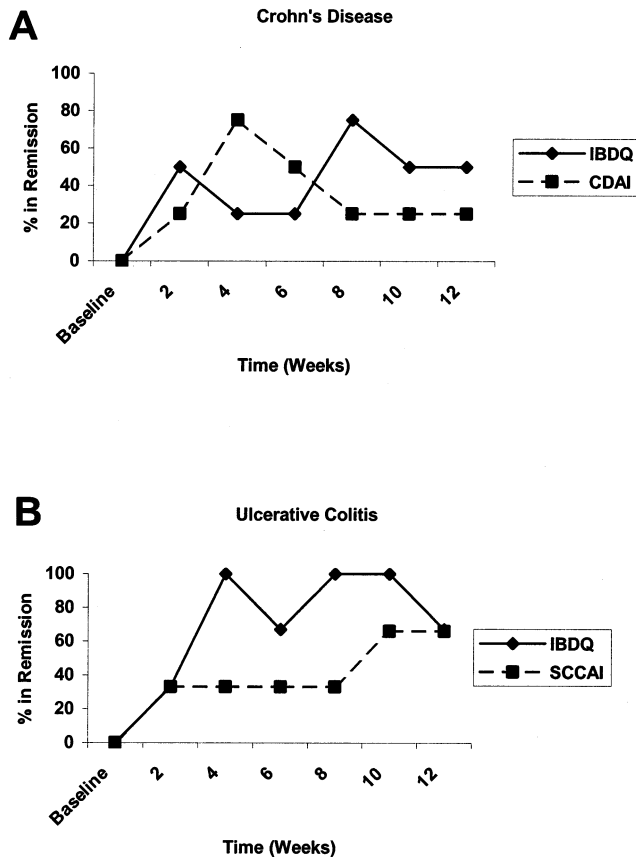
**Table 2.** Change in IBDQ During Treatment and Observation Period

Patient No.	Baseline	wk 2	wk 4	wk 6	wk 8	wk 10	wk 12	wk in Remission
<b>CD</b>								
1	127	199*	102	166	202*	190*	180*	8/12
2	115	134	167	169	179*	185*	198*	6/12
3	54	50	49	52	80	104	79	0/12
4	149	177*	180*	243*	185*	152	140	8/12
<b>UC</b>								
5	138	139	175*	191*	186*	191*	172*	10/12
6	166	176*	188*	146	170*	170*	178*	10/12
7	160	168	190*	175*	182*	182*	166+†	8/12
Mean IBDQ	130	149	150	163	169	168	159	
% in Remission/wk	0%	43%	57%	43%	86%	71%	71%	
Cumulative % in remission	0%	43%	71%	71%	86%	86%	86%	8.3/12

Patient 3 not included in mean.

\* IBDQ  $\geq 170$ .

† + = wk 13 for patient 7.



**Figure 2.** Upper graph (A) shows mean percentage of subjects with Crohn's disease in remission at baseline and at each 2-wk interval as defined by an IBDQ  $\geq 170$  and a CDAI of  $\leq 150$ . Lower graph (B) shows the percentage of subjects with ulcerative colitis in remission at baseline and at each 2-wk interval as defined by an IBDQ  $\geq 170$  and an SCCAI of  $\leq 4$ .

time of 2–4 wk until the majority of patients achieved remission. After the peak effect, the effect of therapy seemed to wane in several of the patients, which was shown as a decreased fraction remaining in remission.

The baseline and biweekly disease activity indices are shown for the patients with CD in Table 3. Remission is usually considered to be a CDAI of  $\leq 150$ , and with this criterion, three of four patients (75%) with CD achieved remission. The patient who did not achieve remission (patient 3), experienced a clinical response manifest by a 153-point reduction in her CDAI at wk 12, but this score did not decrease to  $< 150$ . At the end of the 12-wk treatment and observation period, two of the three patients who went into remission relapsed. In patients with UC, the mean SCCAI was 7.0 at baseline. At 2 wk it decreased to 6.3; at 6 wk it was 5.0; and at 10 and 12 wk it was 4.0. If an SCCAI of  $\leq 4$  is considered to indicate remission, every patient with UC in this study achieved remission during the treatment and observation period, and one patient experienced a relapse.

In inflammatory bowel disease, no single commonly obtainable laboratory study adequately describes the degree of active inflammation. Although active inflammation was observed in all patients at the initial colonoscopy, the baseline C-reactive protein (CRP) was elevated in four of the seven subjects. In patient seven, who had UC, the CRP decreased from 9.0 to 1.5 at the end of the 12-wk period, but the reduction was minimal ( $< 0.4$ ) in the rest. Eosinophilia frequently does not occur in noninvasive helminthic diseases. In this group of patients, the mean baseline eosinophil count was  $102/\text{mm}^3$ . If the highest eosinophil counts throughout the period were averaged, the mean value of highest counts was  $251/\text{mm}^3$  and no individual values were in the abnormal range.

#### Maintenance Period

Multiple doses were given to two patients with CD. Patient 3 had been observed for 1 yr averaging 25 watery stools daily without spontaneous improvement. Colonoscopy demonstrated active disease in the neo-terminal ileum. She consistently complained of arthralgias and chronic fatigue but refused infliximab (Remicade) therapy. In the initial treatment and observation period, she responded briefly to a

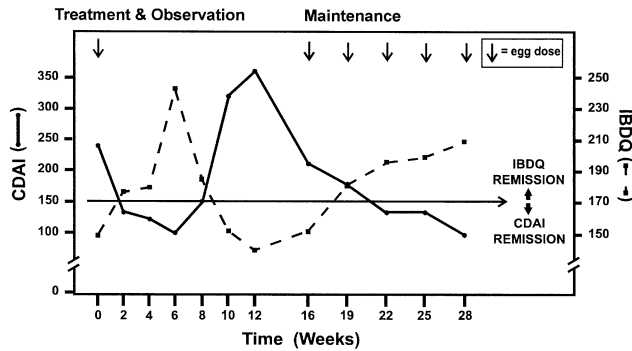
**Table 3.** Effect of Therapy on the CDAI and SCCAI During Treatment and Observation Period

Patient No.	Baseline	wk 2	wk 4	wk 6	wk 8	wk 10	wk 12	wk in Remission
<b>CDAI</b>								
1	341	170	137*	128*	40*	78*	116*	10/12
2	250	270	147*	167	248	212	172	2/12
3	565	661	748	592	581	456	412	0/12
4	243	134*	125*	103*	152	323	360	8/12
Mean CDAI	350	309	289	248	255	267	265	6.7/12
<b>SCCAI (UC)</b>								
5	6	6	5	4*	4*	4*	5	6/12
6	7	3*	3*	5	5	3*	3*	8/12
7	8	10	8	6	5	5	4*	2/12
Mean SCCAI	7.0	6.3	5.3	5.0	4.7	4.0	4.0	
% in Remission/wk	0%	29%	57%	43%	29%	43%	43%	
Cumulative % in remission	0%	29%	57%	71%	71%	71%	86%	5.3 wks

Remission determined by either index (patient 3 not included).

\* CDAI  $\leq 150$  or SCCAI  $\leq 4$ .

† (+ = wk 13 for patient 7).



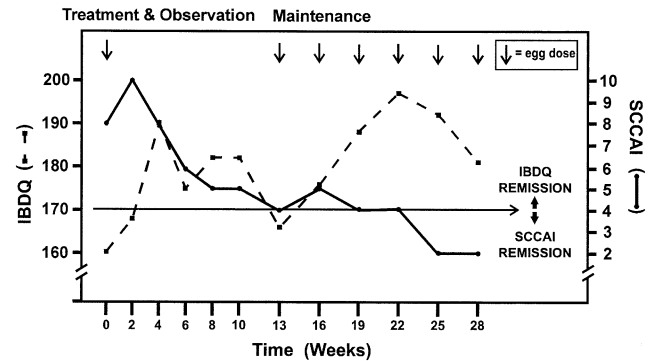
**Figure 3.** This is the early clinical course of a patient (patient 4) with refractory CD who received *T. suis* ova at baseline. Early in the 12-wk treatment and observation period he went into remission, but at 10 wk he developed a significant relapse. At wk 16 he was restarted on a dosing schedule of every 3 wk (maintenance therapy) and entered prolonged remission. The duration of remission is now >1 yr.

single dose of the biological agent. The CDAI dropped 151 points but did not achieve remission (CDAI <150). She was later started on maintenance therapy with *T. suis* at 3-wk intervals. After 18 wk of triweekly therapy, the CDAI fell progressively from 526 to 213 and the IBDQ increased from 74 to 171. The stools became more formed, chronic arthralgias and fatigue resolved, and her only medication was mesalamine. This improvement has persisted for >3 months.

Another patient with CD (patient 4) was treated with *T. suis*, which induced a remission of 2 months' duration (Fig. 3). Several months after relapsing, he was placed on maintenance therapy and received additional doses of eggs at 3-wk intervals. He again achieved remission that has now extended beyond 1 yr. The changes in the IBDQ were roughly and inversely proportional to the changes in CDAI. He has now discontinued all of his medications and feels entirely well. His complaints of chronic fatigue and arthralgias have disappeared.

Multiple doses were also given to two patients with UC. Patient 6 had steroid-dependent UC that remained active on 20 mg/day of prednisone. During phase I this patient received a single dose of 2500 eggs. At 4 wk he was in remission, and his IBDQ rose from a baseline of 166 to 190. The SCCAI decreased from the baseline of 7 to 3 at 2 and 4 wk. However, during wk 6 his disease relapsed (IBDQ score 146, SCCAI 3). At wk 20 he was started on maintenance therapy with egg therapy every 3 wk. He has achieved prolonged remission for >1 yr and was successfully tapered off prednisone.

The course of the IBDQ and SCCAI for patient 7 is outlined in Figure 4. This patient had been treated with prednisone, mesalamine, and azathioprine but had not responded to high dose combination therapy. Proctocolectomy had been recommended but was refused. After ova therapy, he noted gradual and progressive improvement. The SCCAI fell from 8 to 5 after a brief rise to 10, and



**Figure 4.** This is the early clinical course of a patient (patient 7) with refractory ulcerative colitis who received 2500 *T. suis* ova at baseline. At 1 wk after the 12-wk treatment and observation period, he was given repetitive doses at 3-wk intervals as maintenance therapy that has continued to the present. A remission is defined as an IBDQ score  $\geq$ 170. The horizontal line indicates the point of remission for the IBDQ. The arrows indicate when he received ova. The dashed line is his SCCAI score. In the SCCAI, the lower the number the better. He has remained in remission and has been successfully weaned off steroids. The duration of his remission is now >1 yr.

according to the IBDQ, he entered remission. After the initial treat and observe period, he was started on maintenance ova therapy. After taking a dose every 3 wk, he progressively improved. The SCCAI decreased from 8 at baseline to 2 at 25 wk and his IBDQ increased 37 points to 197 at 22 wk. He has continued to do well, remaining in remission now for 1 yr. With continuing triweekly therapy, he has been successfully tapered off prednisone and is maintained only on Asacol (Procter & Gambel Pharmaceuticals, Cincinnati, OH).

## DISCUSSION

### Rationale

Eggs of the porcine helminth, *T. suis*, were administered to patients with active CD and UC. The idea that colonization with helminths might be effective in IBD emerged from the theoretical, epidemiological, and experimental evidence described in the Introduction. This study cannot and should not be interpreted as a study of mechanism. However, it seems that the helminth ova favorably modify and diminish the inflammatory response that occurs in both UC and CD. A study from our laboratory has demonstrated that helminths protect against experimental colonic inflammation (19). A recent study confirmed the ability of helminths to modify *Helicobacter pylori*-induced gastric mucosal inflammation (20). Other mechanisms are also possible, including alteration in the luminal flora (21).

### Safety

The primary goal of this study was to determine whether exposure to *T. suis* is safe in selected IBD patients. Monitoring of standard laboratory data demonstrated no worsening of the values. No significant clinical complications or

adverse events occurred in any of the patients. More than 100 doses have been given to these seven patients without a single adverse effect that can be attributed to the agent, and it was not necessary to treat any of these patients with an anti-helminthic agent for a suspected problem.

### Effectiveness

The patients selected for this study had chronic active symptoms that had not responded to conventional therapy. Several patients had been tried on methotrexate, and one patient had been treated in a controlled clinical trial of rIL-10 without benefit. During the initial treatment and observation period, all patients showed evidence of improvement, as measured by a rise in the IBDQ and a decrease in the CDAI or SCCAI. Patients are usually considered to have achieved remission if they have an IBDQ >170, and all but one patient achieved this value. If the CDAI is <150, CD patients are considered to be in remission. Thus, three of four patients with CD achieved remission and the fourth patient experienced a clinical response with a fall in the CDAI of 153 points. Patients with UC experienced a reduction of the SCCAI to 57% of baseline, and all three achieved remission within 12 wk after a single dose.

Patients improved for a mean duration of about 8 wk. However, the improvement experienced by some patients was temporary, and three of the six patients who achieved remission relapsed within 12 wk after their initial dose according to the CDAI or SCCAI. Although our experience is limited, the prolonged improvement after giving multiple doses to four patients is encouraging. Maintenance therapy given every 3 wk resulted in extended remission, which suggests that repeated doses can be effective in prolonging the benefit.

### Past and Future

Humans have been colonized by helminths since antiquity (22–24). Perhaps elimination of such organisms these has rendered susceptible humans vulnerable to destructive inflammatory diseases such as IBD. We are encouraged that the initial experience with helminth ova therapy has demonstrated no adverse effects from administration of *T. suis* ova and by the improvement experienced by this small group of patients. It remains possible that the observations represent a placebo response. We think that this is unlikely, but we recognize that a larger double blind, placebo-controlled study is important and necessary to establish helminthic colonization as a safe and effective therapy for IBD.

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