IBD LIVE Case Series–Case 4: Worms in IBD: Friend or Foe

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LEARNING OBJECTIVES

After completing this journal-based activity, physicians should be better able to:

1. Define the "hygiene hypothesis" of autoimmune diseases.
2. Understand the reasoning behind *Trichuris suis* ova (TSO) therapy for inflammatory bowel disease.
3. Know the key findings of trials using TSO in patients with Crohn's disease and ulcerative colitis.
4. Be aware of the potential risks regarding helminth therapy.
5. Know the current opinion regarding TSO treatment in inflammatory bowel disease.
6. Be aware of the scope of complementary and alternative medicine (CAM) use in the United States, particularly among individuals with inflammatory bowel disease.

PRESENTATION

Dr. Abhishek Gulati, 2014 to 2015: First Year Fellow in Gastroenterology at Allegheny Health Network

This is a 42-year-old male who was diagnosed with ulcerative colitis in 1995 after presenting with lower abdominal pain, cramping, urgency, and bloody diarrhea. His ulcerative colitis was treated with sulfasalazine and intermittent courses of high dose prednisone for many years. Small bowel follow through was normal. In 2008, he was started on infliximab and did well for 3 years, but stopped on his own and was lost to follow-up. In 2012, he returned with bloody diarrhea, and a colonoscopy was performed that demonstrated active left-sided ulcerative colitis. He was started on adalimumab but, due to lack of response, it was recommended that he undergo a colectomy.

In December, 2014, he presented to our center for a second opinion. For the past 10 months, he has been receiving 40 mg of adalimumab each week and remains on 25 mg of prednisone and mesalamine. The patient's medical and surgical histories are otherwise noncontributory. He is a landscaper who lives with his family at home. He denies alcohol consumption, cigarette smoking, or recreational drug use.

On physical exam, the patient had moon facies and a buffalo hump. His abdomen was soft and nontender, without masses. The remainder of his physical exam was normal. His lab work included complete blood count, chemistry, B 12 level, folate level, liver function tests, C-reactive protein, and erythrocyte sedimentation rate. The C-reactive protein was elevated at 2.7 mg/dL (normal <0.5 mg/dL) and he was anemic with a hematocrit of 37% (normal 42%–54%).

Received for publication November 1, 2015; Accepted February 2, 2016.

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All authors and staff in a position to control the content of this CME activity and their spouses/life partners (if any) have disclosed that they have no financial relationships with, or financial interests in, any commercial organizations pertaining to this educational activity.

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DOI 10.1097/MIB.0000000000000770

On computed tomography scan, there was thickening of the large intestine that was most notable in the descending and sigmoid colon.

A few weeks after his office visit, the patient underwent a colonoscopy. The rectum and descending colon showed continuous areas of ulceration, granularity, and friability (Fig. 1). The proximal colon and terminal ileum were normal. Dr. Hartman, could you review the pathology?

Dr. Douglas J. Hartman

The pathologic findings in this case are nonspecific. You can see that there is active colitis without definitive evidence of chronic mucosal changes (Figs. 2 and 3). These histologic changes may represent an acute infection, drug injury, diverticular disease-associated colitis, or early idiopathic inflammatory bowel disease. Clinical correlation would be required to determine the etiology for what we are seeing histologically.

Dr. Abhishek Gulati

Now, I would like to show you photos of the most interesting part of his colonoscopy. As we progressed the scope through the cecum, we were quite surprised to come upon some small white worms (Figs. 4 and 5). Although we are not aware of any previous infestations, our first thought was that, as a landscaper, perhaps he had gotten the worms through oral transmission from working with dirt and mud.

Dr. Miguel D. Regueiro

Let us stop here for a discussion. The images of the worms are quite impressive. I want to ask my colleagues for their thoughts on this case and specifically about parasites in inflammatory bowel disease (IBD).

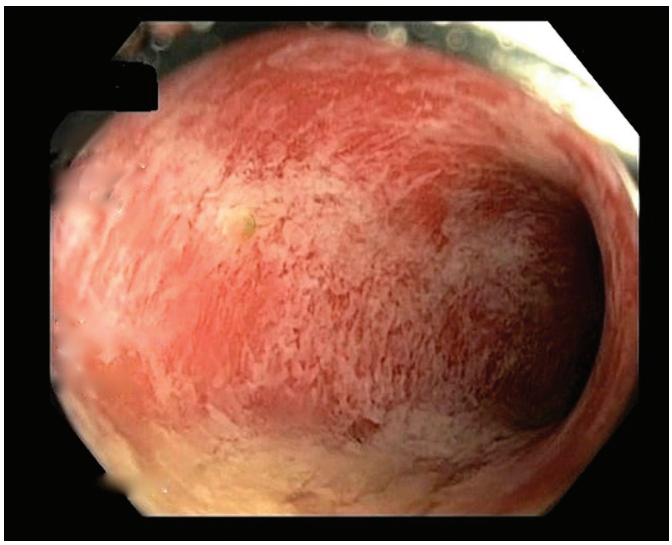

FIGURE 1. Endoscopic image of the descending colon demonstrating ulcerations, granularity, and friability of the colonic mucosa.

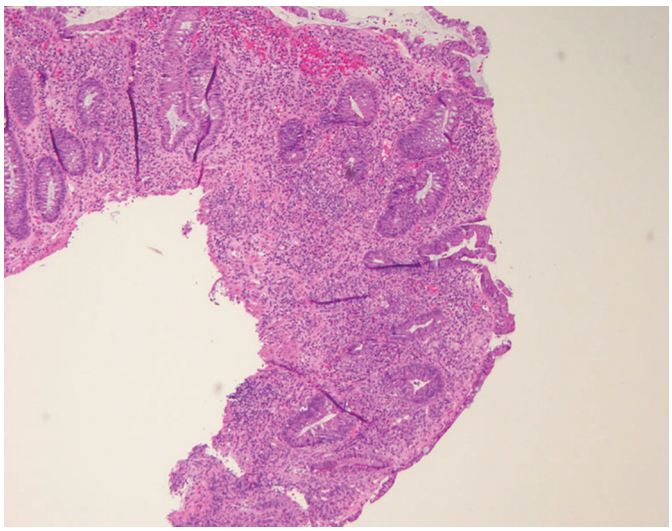

FIGURE 2. Mucosal biopsy from left colon showing active colitis. Increased lymphocytic inflammation suggestive of a lymphoid aggregate is present at the base of the mucosal fragment. Architectural distortion is identified but no evidence of epithelial metaplastic changes or dysplasia is identified (Hematoxylin and eosin, ×40).

Dr. Kofi Clarke

We sent the worms to the lab. As previously stated, the terminal ileum otherwise appeared normal without inflammation. As we were doing the colonoscopy, 2 questions went through my mind: (1) how did he get these worms? and (2) should we treat them or leave them, hoping that they might help with his colitis?

Dr. Miguel D. Regueiro

Dr. Binion, what do you think about worms in IBD? What's the cause? Could they be helpful?

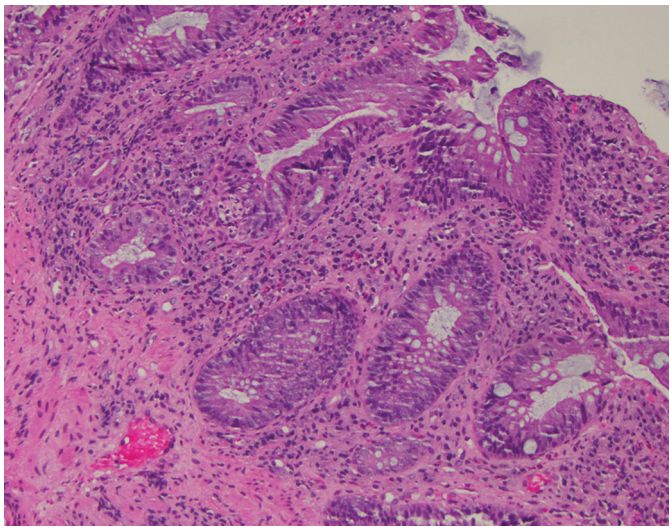

FIGURE 3. Mucosal biopsy from left colon showing active colitis. The colonic glands are sitting on the muscularis mucosa, which argues against chronic mucosal changes. No evidence of epithelial metaplastic changes or dysplasia is identified (Hematoxylin and eosin, ×100).

Dr. David G. Binion

The issue of helminths colonizing the gastrointestinal tract is a state of nature. Humans have been around for about 2 million years and, during the majority of that time, we have had lots of different organisms living inside the lumen of our gastrointestinal tract, including helminths. As humans moved through various stages of civilization into the latter half of the 20th century, we have been dewormed. This occurred probably as the result of public health measures and has paralleled the development of chronic inflammatory diseases, including IBD, asthma, and hay fever, which is probably the mildest version of chronic inflammation on a mucosal surface.

Dr. Joel Weinstock, formerly at the University of Iowa, explored the value of worm treatment in IBD back in the 2003 to 2005 time period. Two of his papers were published in 2005 that evaluated Crohn's disease patients and ulcerative colitis patients that were treated with *T. suis,* the porcine whipworm, eggs, and in both papers there was a clinical response. Given this patient's occupation as a landscaper I wonder if the worms are actually *Trichuris trichiura*, or human whipworm, but I am not a parasitologist.

In terms of worms treating IBD, the initial studies from Iowa were positive and showed that, in subgroup analysis, the combination of *T. suis* ova and azathioprine had a high response rate in patients with Crohn's disease of the terminal ileum. However, our patient has left-sided ulcerative colitis. It is an interesting scenario because I wonder if the worms have been there for some time and that is the reason that the anti-tumor necrosis factor (TNF) has not been successful. I have a suspicion that concomitant immunomodulator therapy, and not anti-TNF therapy, in the setting of a parasitic infection would offer the best chance for clinical response. However, this is not likely in the current patient who has active colitis despite anti-TNF, steroids, and active worm infection.

The trials done by Coronado Bioscience exploring helminth therapy in IBD patients in recent years have not been successful.

Dr. Miguel D. Regueiro

Dr. Farraye, What Are Your Thoughts?

Dr. Francis A. Farraye

As Dr. Binion noted, Coronado Biosciences sponsored a study in moderate to severe Crohn's disease using *T. suis* and although *T. suis* treatment was safe, the primary endpoint of a 100-point decrease in the Colitis Disease Activity Index (CDAI) was not met. A randomized controlled study led by Dr. Stephen Hanauer in patients with left-sided ulcerative colitis is currently being conducted that might provide some insight on this form of therapy *[Note: This study was terminated by its sponsor following the IBD LIVE session]*.

I have seen worms rarely in my IBD patients. In general, the knee jerk reaction is to treat the infection. I am intrigued by David's idea of deferring treatment but, as this patient has worms and is not doing well, I would just eradicate the worms to remove this variable. After eradication, there are a number of things that you can do for this man to try to understand why he is steroid dependent.

Dr. Miguel D. Regueiro

Dr. Brand, would you treat the worms or not treat the worms, that is the question?

Dr. Myron H. Brand

I would treat the worms. These worms may just be a secondary phenomenon from his landscaping and may have nothing to do with his disease whatsoever. And I think that you may be incorrect about previous studies. I think that both Americans and Europeans have looked at the worms fairly extensively and have not found them to be effective.

Additionally, in the studies by Weinstock and his colleagues, I do not think many participants went into remission with primary worm therapy. My sense is that worms are not going to be an effective treatment for IBD, so I would definitely treat the worms. This is an interesting case for me because I had a landscaper who came to me with colitis for a second opinion. We eventually discovered that he had atypical tuberculosis that even involved his knee. Once the tuberculosis was treated, his colitis disappeared.

Dr. Miguel D. Regueiro

When I see worms while performing a colonoscopy—and I have seen a few cases like this one—my initial response is to treat them. They are usually whipworms or pinworms. However, it is an interesting thought that perhaps the worms would be therapeutic for IBD. Overall, as has been stated, the studies in Crohn's disease have been mostly negative thus far. The left-sided ulcerative colitis studies that are underway right now may bring some new data into the picture. Altogether, there is probably less enthusiasm for worms as a primary treatment for IBD than there is a belief that early exposure may help to prevent autoimmune diseases.

Dr. Leonard Baidoo

There is a relationship of early life exposure to worms. If one is exposed to worms at a very young age, it induces an innate, antigenic immune response that may protect the person from the adaptive immune response characteristic of IBD. I think the parasitic infections in children in third world countries may be the reason that IBD is not common there. Therefore, the proper course of action in this patient would be to get rid of the worms because he already has IBD and the preventative effect of worms is too late for him.

Dr. Miguel D. Regueiro

I agree with Dr. Baidoo that worms are probably most useful for IBD prevention and protection but not as a form of primary treatment. Let us get back to the case. What happened next?

Dr. Kofi Clarke

There is definitely more to this story. When the patient woke up, I told him about the worms in his cecum and he said, "Of course you saw worms. I drank these worms 8 months ago." In fact, he imported these worms from Spain. Therefore, the

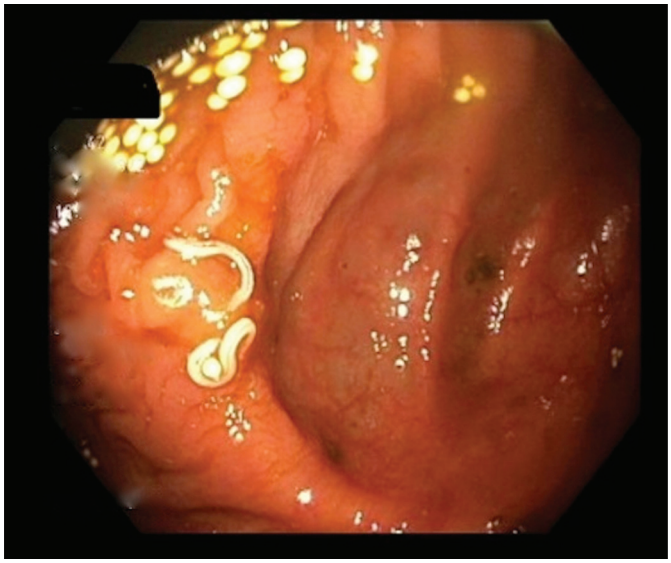

FIGURE 4. Worms observed in the wall of the cecum during colonoscopy. The worms were identified as whipworm (*Trichuris spp*).

parasitic infestation of his colon was done through his purposeful ingestion of worms that he purchased. He has remained on adalimumab and high dose steroids since then.

Dr. Miguel D. Regueiro

As this case demonstrates, our patients frequently participate in various forms of complementary medicine. I think this speaks of 2 issues: (1) the desperation of our patients to find an effective treatment and (2) the sense that "natural" or "complementary" therapies are safer and better than traditional medications. Dr. Clarke does he know which type of worms he ingested?

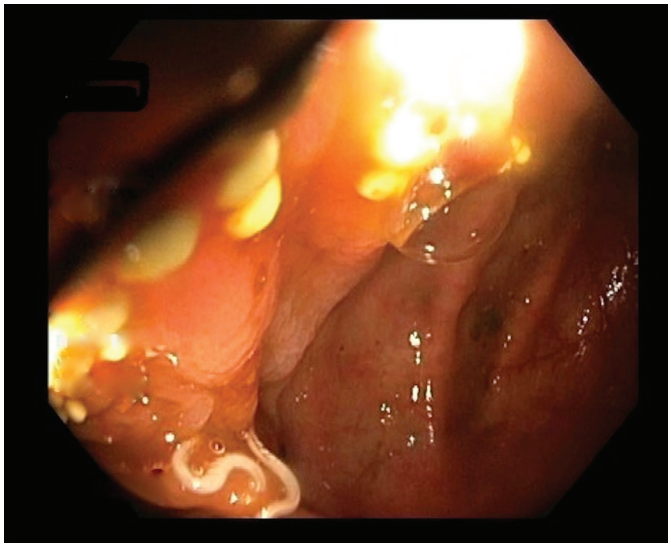

FIGURE 5. A second, closer endoscopic image of whipworms (*Trichuris spp*) that were noted in the patient's cecum.

Dr. Kofi Clarke

Yes, they were porcine whipworms.

Dr. Miguel D. Regueiro

Let us proceed and ask Dr. Gulati to present the final part of this case.

Dr. Abhishek Gulati

This case led me to visit the Internet where I found numerous web sites claiming "miracle cure" for IBD with worms. Our patient was shipped the worms by overnight mail from Europe. The patient had a conference call consultation with the seller of the worms to discuss his illness and the intended use of the worms. He had the option of buying either the pig whipworm, *T. suis,* ova or hookworm larvae that may be applied to the skin.

In 2009, the Food and Drug Administration defined helminths as biological products that could not be marketed without having undergone clinical trials. The Food and Drug Administration has since banned the sale of helminths in the United States so the companies that sell these organisms are now located outside of the United States. Because the helminth ova must go through 3 life cycles outside of the body before becoming infective, it is believed that regular hand hygiene should be sufficient to keep from infecting other people.

Dr. Miguel D. Regueiro

Dr. Wolf Schraut, let us get a surgical perspective on this case. You have a patient with severe left-sided ulcerative colitis who ingested worms and has evidence of worms in his cecum on colonoscopy. What are your thoughts?

Dr. Wolfgang H. Schraut

I think this patient has severe colitis. He has failed 2 anti-TNFs and is steroid-dependent. He will need a total proctocolectomy. I do not think the worms are helping him. I also do not think that operating on him with the worms in the colon will present a problem, but I would favor eradication of the worms first and then surgery because there is always a slight chance of worm migration through suture lines and anastomoses.

Dr. Kofi Clarke

I agree with Dr. Schraut that this patient should undergo surgery. However, he has been adamantly opposed. We treated the worms with albendazole and initiated vedolizumab with a plan to repeat the colonoscopy in 6 months. If he is worse or shows no improvement at colonoscopy, we told him that we have no other recommendation than a colectomy.

Dr. Miguel D. Regueiro

It is interesting that some patients are willing to undergo an alternative treatment that has been banned by the Food and Drug Administration outside of controlled clinical trials. Dr. Cross, you wanted to make a comment?

Dr. Raymond K. Cross

To me, the critical thing is that he did not disclose that he was doing this. We know that patients use complementary and alternative medicines. It is frightening that this patient got worms from Europe without telling any of his doctors. I do not specifically ask patients about worms or any other off the beaten path therapies. Perhaps the take home message of this case is that it is important to ask patients who are new referrals about any alternative therapies that they may be using. I wonder if I were to ask my patients, how many of them would have actually tried worm therapy.

Dr. Miguel D. Regueiro

Drs. Farraye, Brand, and Binion, let us get your final thoughts.

Dr. Francis A. Farraye

Treatment-wise, I would have done exactly the same thing. First, I would have eradicated the worms. I would have checked his adalimumab level and, if therapeutic, I would have switched him to vedolizumab given his previous history. I also believe that he will need surgery if the vedolizumab does not work.

Dr. Myron H. Brand

I would also get rid of the worms and switch him to vedolizumab and recommend surgery if he fails.

Dr. David G. Binion

The cases we have discussed today highlight the fact that IBD is not a one-size-fits-all condition. There are going to be small subgroups of patients that are able to respond to different approaches. The data from Dr. Joel Weinstock and the pilot studies from Iowa showed that there might be some signal here that could be advantageous to some patients. I think that their work could be a clue that certain factors coming from the lumen might drive immune responses that could be beneficial in certain settings.

I agree with Dr. Cross that our patients need to tell us about any complementary therapies they may be taking to give them the best chance of achieving an optimal response.

DISCUSSION

The role of environmental influences on the risk of IBD is well recognized.[1] For instance, the incidence of IBD has been shown to be lower among people whose jobs involve exposure to dirt and soil.[2] Within the United States, studies have observed that disease is less prevalent in people brought up in rural, southern parts of the United States.[3] Underdeveloped and developing countries in Asia and Africa have a lower incidence of IBD compared with the developed world and this difference cannot be explained by genetics alone.[4] Second-generation immigrants from these same regions have an incidence of IBD that approximates the native population, supporting the theory that there is an environmental trigger to the disease.[5,6] Other immunological diseases (such as multiple sclerosis and various allergies) show a similar inverse relationship between their incidences in comparison to the incidence of helminth infections.[7–10]

These observations formed the foundation of the "hygiene hypothesis" for immunoregulatory illnesses.[10–12] According to this theory, less sanitary environmental conditions in underdeveloped countries correlate with greater exposure to pathogens, including helminths, with the effect of priming the immune system and diminishing the susceptibility to immune-related conditions such as IBD.[11] Helminth infections drive the T cell differentiation into the Th-2 pathway, causing plasma cells to secrete IgE, and leading to eosinophilia and elevated Th2 cytokines (e.g., interleukin [IL] 4, 10, 13).[13,14] It is known that the Th-1 cytokines interferon-gamma and TNF-alpha perpetuate the characteristic inflammation of Crohn's disease and ulcerative colitis. The production of Th-1 cytokines may be suppressed when a vigorous Th-2 immune response is present. Thus, helminth infections early in life may reduce an individual's susceptibility to IBD.[15]

There are a number of important questions to address:

1. Is there a role for helminth therapy in IBD and is there any evidence to support its use?
2. What is the safety data regarding treatment with helminths?
3. Is helminth therapy safe with concomitant immunosuppression?

Helminth therapy for IBD may be defined as oral administration of porcine species helminthic eggs/larvae causing a controlled transient infestation in the patient, with the goal of generating a durable host immune response.

The data supporting the use of helminth therapy for IBD are limited. A 2005 double-blind, randomized placebo-controlled trial conducted between 2001 and 2003 by University of Iowa researchers showed that patients with ulcerative colitis treated with 2500 TSO administered orally every 2 weeks for 12 weeks were more likely to achieve an improvement in Ulcerative Colitis Disease Activity Index (UCDAI) than those given a placebo (43% in ova group versus 16% in placebo group).[16] No side effects were noted among the 30 patients in the treatment arm or the 24 patients receiving placebo. Patients with total colonic involvement and shorter duration of disease were more likely to show improvement. Fourteen of the 30 (47%) patients in the treatment arm were on systemic corticosteroids, azathioprine/6-mercaptopurine or both at enrollment, and none experienced overt complications that could be attributed to ova treatment. Notably, the difference in the proportion of patients that achieved a UCDAI of 0 to 1 was not significant between the 2 groups.

Also in 2005, the results of an uncontrolled, open-label study of 29 patients with active Crohn's disease, defined as a CDAI >220 were published by Summers et al[17] at the University of Iowa. Patients were given 2500 TSO every 3 weeks for 24 weeks. At 24 weeks, almost 80% of patients had a response (defined as reduction in CDAI by 100 points) and 73% of patients achieved a CDAI <150, which was classified as remission. Many

of these patients were on steroids and azathioprine or 6-mercaptopurine before enrolling, but none was noted to experience significant side effects. Interestingly the study showed that patients with an intact terminal ileum fared better than those who had undergone terminal ileal resection (80% remission rate versus 40%). Patients who were taking immunosuppressants at baseline achieved a better response at 24 weeks compared with those not on immunosuppressants (12 patients [85%] versus 9 patients [60%]). The improved response for patients on immunosuppressants was inferred to occur because these medications may have dampened an immune response that allowed for colonization with the worms. None of the results of subset analyses achieved statistical significance.

A separate, small randomized placebo-controlled trial published in 2013 by Sandborn et al[18] assessed the safety of administering a single escalating dose (500, 2500 and 7500 TSO) to 3 separate groups of patients with Crohn's disease. In the active arms, 12 patients were randomized to 1 of the 3 groups, and were followed for 6 months after dose administration. The study's primary goals were establishing the safety and tolerability of administering ova to the patients. No short-term (2 weeks) or long-term (6 months) adverse events were noted. Similar to previous studies of TSO, several patients were on systemic corticosteroids, azathioprine and/or 6-mercaptopurine at the time of the trial.

In conjunction with development partner Dr. Falk Pharma GmbH, Coronado Biosciences (now Fortress Biotech) conducted 2 larger clinical trials evaluating TSO therapy in patients with Crohn's disease.[19–21] Coronado's TRUST-I (TRichUris Suis ova Trial) was a 12-week, phase 2 study conducted in 250 US patients with moderate-to-severe Crohn's disease that examined the effects of TSO compared with placebo on the induction of response, as measured by CDAI.[19] Randomization was based on patient CDAI at enrollment. Results demonstrated that the study did not meet the primary endpoint of improving response, defined as a 100-point decrease in CDAI, or the essential secondary endpoint of remission, which was defined as achieving a CDAI <150 points. The lack of response to TSO was driven mainly by a higher than expected placebo response among patients with CDAI <290. TSO did demonstrate a nonsignificant improved response in patients with CDAI >290.

TRUST-II, also known as the Falk trial, was a double-blind, randomized, placebo-controlled, multi-center phase 2 study that assessed 3 different dosages of oral TSO in 240 European patients with moderate-to-severe, active Crohn's disease.[20] The study intended to include two 12-week periods, namely an initial 12 weeks evaluating safety/efficacy followed by a 12-weeks open-label treatment period with TSO. However, secondary interim data analysis conducted by an independent data monitoring committee recommended that the trial be stopped because of lack of efficacy.[22] In April, 2015, Coronado Biosciences announced that it would no longer pursue the development of its TSO program.[23] In a rebranding maneuver, the company changed its name to Fortress Biotech 1 week after this announcement.[24]

A 2014 Cochrane meta-analysis summarized the available evidence regarding helminth therapy in IBD patients.[25] The authors included randomized controlled trials where helminths were the intervention among patients with Crohn's disease or ulcerative colitis. Their primary outcome was induction of remission while secondary outcomes included clinical, histologic, or endoscopic improvement as defined by the authors, endoscopic mucosal healing, change in CDAI or UCDAI, change in quality of life score, hospital admissions, requirement for intravenous corticosteroids, surgery, study withdrawal, and the incidence of adverse events. Overall, the quality of evidence was felt to be insufficient to make any firm conclusions regarding the efficacy of TSO for Crohn's disease or ulcerative colitis. The clinical trial of TSO for left-sided ulcerative colitis that was mentioned during this case conference was terminated early by its sponsor, Coronado Biosciences.[26] However, investigators at New York University School of Medicine are currently conducting a separate 24-week randomized double-blind placebo-controlled clinical trial in ulcerative colitis patients in efforts to characterize immune mechanisms of the intestinal mucosa, particularly mucus production and T-regulatory effector lymphocyte populations, and their response to TSO therapy.[27] Results of this trial may provide guidance as to whether IBD patients may benefit from this form of treatment.

Although these few studies may not have observed deleterious effects of helminth therapy, some investigators have argued of the potential for harm, particularly because mucosal damage and disruption of the muscularis mucosa in IBD may permit the penetration of larvae into the bowel wall; additionally, these types of parasites have unpredictable journeys in atypical hosts, occasionally being found in the lungs and liver.[28,29] A 2006 case report describes a 16-year-old boy with active Crohn's disease who had failed to respond to numerous medications, including azathioprine and adalimumab.[30] Thereafter, he received 5 oral doses of 2500 TSO off-label and demonstrated signs of persistent infection 6 months later. Although *T. Suis* does not typically complete its life cycle in humans, the rare chance of colonization or persistent infection has led some clinicians to recommend giving antiparasitic medications to study participants who do not respond to treatment.[31]

Trials of helminth therapy have not been without pitfalls. In a study published in 2011 among Danish individuals with allergic rhinitis, 49 adults who ingested 2500 TSO every 3 weeks for 4 months experienced a 3- to 19-fold higher rate of episodes of moderate to severe flatulence, diarrhea, and upper abdominal pain than the 47 participants receiving placebo.[32] The reactions lasted up to 2 weeks. Similar side effects of TSO treatment may not have been as obvious among studies of patients with active IBD because of their underlying baseline gastrointestinal symptoms. It is also important to recognize that clinical trials evaluating helminth therapy operate in accordance with informed consent and stringent institutional review board regulations, as well as the oversight of qualified health professionals and independent data monitoring. Additionally, there are numerous exclusion criteria in larger clinical trials. For instance, the Coronado Biosciences trials of Crohn's disease patients excluded those with

stricturing disease, ileostomy, abscess/fistulae, upper gastrointestinal involvement, resection of more than 50 cm of the ileum, primary nonresponders to anti-TNFs, patients refractory to azathioprine/6-mercaptopurine, and numerous other factors that are fairly common among IBD patients, particularly those with longer duration or more severe disease.

CASE FOLLOW-UP

Eight months after this case was presented, the patient is in clinical remission on vedolizumab and has returned to the care of his referring gastroenterologist. He is scheduled for a colonoscopy to document his endoscopic response.

EDITOR'S COMMENT

Complementary and alternative medicine (CAM) is used by a significant portion of the US population. In a study conducted by the Centers for Disease Control and Prevention's National Center for Health Statistics, approximately 4 out of 10 adults had used CAM therapy in the past 12 months.[33] Although the exact percentage of IBD patients who use these therapies is unknown, previous work has demonstrated that use of CAM is common among IBD patients attending outpatient clinics.[34,35] About 90% of treating physicians perceive that a majority of their IBD patients were reluctant to bring up the topic of CAM although IBD patients may feel more comfortable discussing their use of CAM with nurses rather than physicians.[35,36]

Certain CAM therapies such as progressive relaxation pose no apparent risks to the patient. Nonregulated biological organisms, such as the helminths that were acquired and ingested by this patient, may have any number of untoward side effects. Although numerous web sites tout the plausible health benefits of "worm therapy" to people with IBD,[37,38] they also acknowledge that potential, short-term problems such as intestinal upset, fatigue, fever, and joint pain may occur, and provide the disclaimer—"Because this is an experimental therapy no one can know how safe it is."[39] The paramount question regarding helminth therapy should not be whether it is safe for IBD patients but, rather, whether it is capable of producing any lasting health benefits. Nonetheless, the concept of altering the immune-mediated milieu from an adaptive to an innate immune response is intriguing. Given the clear hygiene hypothesis of IBD and the apparent protective effect against autoimmune diseases in people exposed to helminths early in life, helminths may one day be a valuable treatment option. At the current time, however, evidence does not support this form of therapy.

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CME-MOC EXAM—22.6
"IBD LIVE Case Series-Case 4: Worms in IBD: Friend or Foe"

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LEARNING OBJECTIVES

After completing this journal-based activity, physicians should be better able to:
1. Define the "hygiene hypothesis" of autoimmune diseases.
2. Understand the reasoning behind TSO therapy for inflammatory bowel disease.
3. Know the key findings of trials using TSO in patients with Crohn's disease and ulcerative colitis.
4. Be aware of the potential risks regarding helminth therapy.
5. Know the current opinion regarding TSO treatment in inflammatory bowel disease.
6. Be aware of the scope of complementary and alternative medicine use in the United States, particularly among individuals with inflammatory bowel disease.

1. The hygiene hypothesis postulates that:
   a. More developed nations have better hygiene that leads to fewer diseases.
   b. Innate immunity is primed by exposure to pathogens early in life, and may explain why more developed countries have higher rates of IBD.
   c. Individuals living in underdeveloped nations have a greater incidence of autoimmune illnesses due to more frequent colonization with parasites.
   d. Nations with better hygiene have better methods of diagnosing diseases, which explains their higher prevalence of IBD and asthma.

   Please see the following references for further study:
   1. Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989;299:1259–1260.
   2. Elliott DE, Urban JJ, Argo CK, et al. Does the failure to acquire helminthic parasites predispose to Crohn's disease? *FASEB J* 2000;14:1848–1855.
   3. Weinstock JV, Summers RW, Elliott DE, et al. The possible link between de-worming and the emergence of immunological disease. *J Lab Clin Med* 2002;139:334–338.

2. The FDA categorizes therapeutic helminth ova and larvae as:
   a. Biologics.
   b. Food, in the category of supplements.
   c. Drugs.
   d. Food, in the category of eggs.

   Please see the following references for further study:
   1. U.S. Food and Drug Administration. Vaccines, Blood & Biologics. Available at: http://www.fda.gov/BiologicsBloodVaccines/default.htm.
   2. Scholmerich J. Trichuris suis ova in inflammatory bowel disease. *Digestive Diseases* 2013;31:391–395.

3. The greatest limitation of the 2005 study by Summers et. al (*Trichuris suis* therapy for active ulcerative colitis: a randomized controlled trial. Gastroenterology 2005;128:825–32.) that evaluated therapy with 2500 *T. suis* ova (TSO) was that:
   a. The treatment arm included only 30 participants.
   b. Only patients with pancolitis were included in the study.
   c. Patients could not be taking steroids during the study.
   d. Only nonsmokers were included in the study.

   Please see the following reference for further study:
   Summers RW, Elliott DE, Urban JF Jr, et al. Trichuris suis therapy for active ulcerative colitis: a randomized controlled trial. *Gastroenterology* 2005;128:825–832.

4. Which of the following statements is true?
   a. A large-scale study conducted by the Centers for Disease Control and Prevention's National Center for Health Statistics found that 10% of US adults reported using CAM in the previous 12 months.
   b. Supporting evidence of the benefits of CAM can be found in countless clinical trials.
   c. IBD specialists have noted that their patients seem forthright in discussing their use of CAM.
   d. It is important for patients to disclose their use of CAM because these therapies can interact with conventional medicines, impacting a patient's illness.

   Please see the following references for further study:
   1. Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. *National health statistics reports* 2008:1–23.
   2. Lindberg A, Fossum B, Karlen P, et al. Experiences of complementary and alternative medicine in patients with inflammatory bowel disease - a qualitative study. *BMC Complementary & Alternative Medicine* 2014;14:407.
   3. Opheim R, Bernklev T, Fagermoen MS, et al. Use of complementary and alternative medicine in patients with inflammatory bowel disease: results of a cross-sectional study in Norway. *Scandinavian Journal of Gastroenterology* 2012;47:1436–1447.
   4. Gallinger ZR, Nguyen GC. Practices and attitudes toward complementary and alternative medicine in inflammatory bowel disease: a survey of gastroenterologists. *Journal of Complementary & Integrative Medicine* 2014;11:297–303.

5. A 2014 Cochrane Database meta-analysis reported that:
   a. TSO should only be recommended for patients with left-sided colitis.
   b. TSO are only effective for IBD patients who concomitantly take an immunomodulator.
   c. There is not enough evidence to recommend TSO therapy for IBD patients.
   d. There is evidence that TSO therapy is effective treatment for both ulcerative colitis and Crohn's disease.

   Please see the following reference for further study:
   Garg SK, Croft AM, Bager P. Helminth therapy (worms) for induction of remission in inflammatory bowel disease. *Cochrane Database of Systematic Reviews* 2014;1:CD009400.

6. Complementary and alternative medical therapies:
   a. May benefit patients through physiologic mechanisms.
   b. May benefit patients due to the placebo effect.
   c. May harm patients.
   d. May have no effect on a patient.
   e. All of the above.

   Please see the following references for further study:
   1. Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. *National health statistics reports* 2008:1–23.
   2. Van Kruiningen HJ, West AB. Potential danger in the medical use of Trichuris suis for the treatment of inflammatory bowel disease. *Inflammatory Bowel Diseases* 2005;11:515.
   3. Opheim R, Bernklev T, Fagermoen MS, et al. Use of complementary and alternative medicine in patients with inflammatory bowel disease: results of a cross-sectional study in Norway. *Scandinavian Journal of Gastroenterology* 2012;47:1436–1447.
   4. Bager P, Kapel C, Roepstorff A, et al. Symptoms after ingestion of pig whipworm Trichuris suis eggs in a randomized placebo-controlled double-blind clinical trial. *PLoS ONE [Electronic Resource]* 2011;6:e22346.

7. In a double-blind, randomized placebo-controlled trial of TSO in Crohn's disease patients conducted by Summers and other researchers at the University of Iowa (*Trichuris suis* therapy in Crohn's disease. Gut 2005;54:87–90), remission was defined as:
   a. Patients' ability to discontinue immunomodulators and steroids.
   b. A CDAI of <150.
   c. Lack of endoscopic evidence of disease.
   d. Complete mucosal healing.

   Please see the following reference for further study:
   Summers RW, Elliott DE, Urban JF Jr, et al. Trichuris suis therapy in Crohn's disease. *Gut* 2005;54:87–90.

8. The TRUST-I (*TRichUris Suis* ova-I) trial phase 2 study evaluating 12 weeks of TSO therapy in 250 US patients with moderate-to-severe Crohn's disease:
   a. Met the primary endpoint of a 100-point decrease in CDAI in the treatment arm.
   b. Met the secondary endpoint of remission, which was defined as achieving a CDAI <150 points.
   c. Demonstrated a nonsignificant improvement in response among patients with CDAI >290 at baseline.
   d. Noted a smaller than expected placebo response.

   Please see the following reference for further study:
   Efficacy and Safety of Trichuris Suis Ova (TSO) as Compared to Placebo (TRUST-I). A Phase II Study to Evaluate the Efficacy and Safety of 12 Weeks of Treatment With Oral CNDO 201 Trichuris Suis Ova Suspension (TSO) as Compared to Placebo, Followed by a 12 Week Open-label Treatment Period in Patients With Moderately to Severely Active Crohn's Disease. ClinicalTrials.gov Identifier NCT01576471. https://clinicaltrials.gov/ct2/show/NCT01576471?term=Trust-1&rank=2. Accessed October 14, 2015.

9. Interim data analysis of the TRUST-2 (*TRichUris Suis* ova-II) trial:
   a. Showed significantly greater improvement in patients receiving TSO rather than placebo.
   b. Noted significant safety concerns among participants that received the highest dose of TSO.
   c. Showed lack of efficacy that led an independent data monitoring committee to recommend study termination.
   d. Demonstrated an underpowered sample size calculation that led an independent data monitoring committee to recommend recruiting a larger number of study participants.

   Please see the following reference for further study:
   Trichuris Suis Ova (TSO) Suspension Versus Placebo in Active Crohn's Disease (TRUST-2). Double-blind, Randomised, Placebo-controlled, Multi-centre Phase II Study to Evaluate the Efficacy and Safety of Three Different Dosages of Oral Trichuris Suis Ova (TSO) Suspension in Active Crohn's Disease. ClinicalTrials.gov Identifier NCT01279577. https://clinicaltrials.gov/ct2/show/record/NCT01279577. Accessed October 14, 2015.