Summer 8-9-2014

The Efficacy and Safety of Trichuris suis Helminth Therapy in the Treatment of Inflammatory Bowel Disease

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The Efficacy and Safety of Trichuris suis Helminth Therapy in the Treatment of Inflammatory Bowel Disease

Abstract
Background: Inflammatory bowel disease (IBD) refers to a group of disorders causing chronic relapsing inflammation of the gastrointestinal tract. The highest incidence of IBD occurs in Europe and North America with more than 2 million affected. The hygiene hypothesis suggests improved sanitation and eradication of parasitic infections in industrialized nations may explain the epidemiologic predilection of disease. Helminths are parasitic worms that diminish immune responsiveness and inflammation in animal studies. Epidemiologic data also suggests that helminths have a protective role in the development of IBD. Trichuris suis is a type of helminth traditionally found in pigs. In humans, it has never been found to cause disease. Is Trichuris suis helminth therapy (TSO) effective and safe in the treatment of inflammatory bowel disease?

Methods: An exhaustive literature search to identify relevant published papers was conducted using the databases Medline-OVID, CINAHL, Web of Science, and PubMed using the keywords: inflammatory bowel disease, Crohn's disease, ulcerative colitis, helminths, and Trichuris. Articles with primary data were included if they addressed the safety and/or efficacy of Trichuris suis ova therapy for IBD. Relevant articles were assessed for quality using the GRADE criteria.

Results: Two randomized controlled trials and two observational case series reports fit the inclusion criteria. All of the studies demonstrated clinical improvement in the indices traditionally used to monitor disease activity in Crohn's disease and ulcerative colitis. No adverse effects were associated with TSO therapy.

Conclusion: Epidemiologic data, animal studies, and the abovementioned human trials all demonstrate that TSO is an effective and safe therapy in the treatment of IBD. However, current clinical trials have released preliminary data that show lack of efficacy. Until data from these trials can be further evaluated, a strong recommendation for TSO cannot not be made.

Keywords: Trichuris suis, Crohn's disease, ulcerative colitis, inflammatory bowel disease, helminths

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

Keywords
Trichuris suis, Crohn's disease, ulcerative colitis, inflammatory bowel disease, helminths

Subject Categories
Medicine and Health Sciences

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The Efficacy and Safety of *Trichuris suis* Helminth Therapy in the Treatment of Inflammatory Bowel Disease

Chelsea Johnson

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 9, 2014

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Biography

Chelsea Johnson is a native of central Oregon where she majored in General Sciences with emphasis in Biology, Chemistry and Psychology. She has worked as an animal behaviorist, naturalist, and mental health technician before entering PA school. She plans to practice Family Medicine in the Pacific Northwest.
Abstract

Background: Inflammatory bowel disease (IBD) refers to a group of disorders causing chronic relapsing inflammation of the gastrointestinal tract. The highest incidence of IBD occurs in Europe and North America with more than 2 million affected. The hygiene hypothesis suggests improved sanitation and eradication of parasitic infections in industrialized nations may explain the epidemiologic predilection of disease. Helminths are parasitic worms that diminish immune responsiveness and inflammation in animal studies. Epidemiologic data also suggests that helminths have a protective role in the development of IBD. *Trichuris suis* is a type of helminth traditionally found in pigs. In humans, it has never been found to cause disease. Is *Trichuris suis* helminth therapy (TSO) effective and safe in the treatment of inflammatory bowel disease?

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Conclusion: Epidemiologic data, animal studies, and the abovementioned human trials all demonstrate that TSO is an effective and safe therapy in the treatment of IBD. However, current clinical trials have released preliminary data that show lack of efficacy. Until data from these trials can be further evaluated, a strong recommendation for TSO cannot be made.

Keywords: Trichuris suis, Crohn’s disease, ulcerative colitis, inflammatory bowel disease, helminths
Acknowledgements

To Jeff Newman: Thank you for your love and support during this rollercoaster of a journey. You changed everything in your life to help me pursue the betterment of our lives together. I owe you a great debt, which I’m sure will be repaid in free ski days each winter.

To my parents: Thank you for always telling me that I am capable of doing anything I set my mind to and supporting me in my decisions. You taught me that honesty and integrity are values that make a person succeed in work and in life. Thank you for always showering me with love and encouragement.
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List of Abbreviations

CBC................................................................................Complete Blood Count
CD................................................................................Crohn’s Disease
CDAI..............................................................................Crohn’s Disease Activity Index
IBD................................................................................Inflammatory Bowel Disease
IBDQ..............................................................................Inflammatory Bowel Disease Quality of Life Index
SCCAI..............................................................................Simple Clinical Colitis Activity Index
TEAEs.............................................................................Treatment Emergent Adverse Events
TSO................................................................................Trichuris suis ova
UC................................................................................Ulcerative Colitis
UCDAI..........................................................................Ulcerative Colitis Disease Activity Index
The Efficacy and Safety of *Trichuris suis* Helminth Therapy in the Treatment of Inflammatory Bowel Disease

**BACKGROUND**

Inflammatory bowel disease (IBD) refers to a group of disorders causing chronic relapsing inflammation of the gastrointestinal tract. The two forms of IBD, ulcerative colitis (UC) and Crohn’s disease (CD) are categorized based on the degree and location of intestinal inflammation. Ulcerative colitis is characterized by diffuse mucosal inflammation of the rectum and colon while Crohn’s disease can affect any part of the gastrointestinal tract, causing patchy transmural inflammation. The symptoms of IBD are greatly varied and include abdominal pain, diarrhea, weight loss, rectal bleeding, and fever. Both diseases are characterized by periods of symptomatic flare-ups and remission. While the precise cause of IBD is unknown, it is thought by researchers that the disease results from a combination of defects in host interactions with intestinal microbiota, intestinal epithelial dysfunction, and aberrant mucosal immune responses to contents within the intestine. Genetic and environmental factors are also thought to play an important role in the pathogenesis of IBD.

The highest incidence of IBD occurs in industrialized Western countries with more than 2 million affected people in Europe and North America. In the last century, there has been a steady increase of IBD in developed countries. Originally developed by Stachan, the “hygiene hypothesis” theory suggests a relationship between a higher incidence of immune mediated disease with improved amenities, smaller family size, and higher standards of personal cleanliness of westernized societies. In the 1990s, Weinstock and Elliot suggested that children raised in extremely hygienic environments are predisposed to immunological diseases later in
life. Their “IBD hygiene hypothesis” further speculated that in hygienic environments there is a lack of exposure to intestinal parasites called helminths, which has contributed to the development of IBD.⁶

Humans have been co-evolving with parasites for most of history. Found in greater than one-third of the world’s population, helminths are a broad group of parasitic worms spread through contact with contaminated soil, water, or food.⁷ Researchers conducted studies⁸ on animals based on the idea that helminths may have a useful role in the responses initiated by the immune system. Initial investigations into the therapeutic use of helminths showed both a protective and therapeutic benefit of helminths given to colitis inflicted laboratory mice. Epidemiological data⁹ show an inverse relationship between the incidence of IBD and helminth exposure, suggesting that helminth infection may have a protective role and prevent IBD from developing. In their South African case control study, Chu et al¹⁰ found that childhood helminth infection was protective against the development of IBD.

Helminthic infections are thought to alter the host immune response in several ways. Joel Weinstock is a medical doctor from Tufts University and recognized worldwide for his extensive research in the study of helminths for the treatment of IBD. He explains that helminths cause changes that induce activation of regulatory T cells involved in dampening immune responses and curbing autoimmunity. They also influence other cells that prevent the activation of effector T cells which lead to inflammation and disease. Finally, the worms appear to influence the intestinal microflora by altering bacterial composition and promoting bacteria responsible for maintaining intestinal health.¹¹ Based on the successful use of helminths in animal models, Weinstock and colleagues⁴ searched the helminths for a species that could be therapeutically used in humans. They found Trichuris suis, a type of whipworm found in pigs and closely related
to the human whipworm *Trichuris trichuria*. This microscopic parasite was thought to be an ideal candidate for human use based on the characteristics that it does not migrate beyond the intestines, reproduce within its host, or transmit from one human host to another. Furthermore, pig farmers that have been chronically exposed to the *T. suis* parasite never develop human disease. The parasite can be harvested from pathogen-free pigs and administered to human patients through ingestion of *Trichuris suis* ova (TSO).

Epidemiologic studies and animal models support the relationship of helminths and the development of IBD. Safety profiles encourage the use of *T. suis* as a possible therapeutic use of helminth infection in human hosts. Is *Trichuris suis* helminth therapy effective and safe in the treatment of inflammatory bowel disease?

**METHODS**

An exhaustive medical literature search to identify potentially relevant published papers was conducted using the databases Medline-OVID, CINAHL, Web of Science and PubMed using the keywords: inflammatory bowel disease, Crohn’s disease, ulcerative colitis, helminths, and Trichuris. The search was further narrowed to include articles in the English language and human studies. The bibliographies of included articles were also screened for additional relevant sources. Articles with primary data were included if they addressed the safety and/or efficacy of *Trichuris suis* therapy for inflammatory bowel conditions. Relevant articles were assessed for quality, validity, and risk of bias using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE). A search of the National Institute of Health clinical trials website revealed two ongoing trials investigating the use of *Trichuris suis* for Crohn’s disease.
RESULTS

The initial search generated 52 articles for review. Duplicates were removed and the remaining articles were screened for primary data studies. Four remaining studies met inclusion criteria. Two studies are randomized control trials\textsuperscript{14,15} and two are observational case series reports.\textsuperscript{16,17} See Table 1.


This randomized, double-blind, placebo-controlled trial\textsuperscript{14} evaluated the safety and tolerability of single, escalating doses (500, 2500, and 7500) of TSO therapy versus placebo in patients with Crohn’s disease. Thirty-six patients between the ages of 20-54 years were recruited from six different US sites and split into three different cohorts of 12. The treatment to placebo ratio was 3:1 respectively, resulting in 27 patients receiving therapy and 9 receiving placebo. The first cohort received 500 TSO or placebo. Upon completion of a 2-week follow-up for cohort 1, the second cohort received 2500 TSO or placebo. After 2 weeks of follow-up for cohort 2, the final cohort received 7500 TSO versus placebo. In this manner the therapy could be investigated for the safety and tolerability of different doses of therapy. Safety and tolerability were evaluated by monitoring the emergence of treatment emergent adverse events (TEAEs) during the study period of 14 days and at month 1, 2 and 6 for follow-up.\textsuperscript{14}

Patients with confirmed Crohn’s disease of at least 3 months duration and between the ages of 18-55 years old were invited to participate in the study. Concomitant use of oral sulfasalazine, mesalazine (5-ASA), mesalazine derivatives, oral prednisone, and azathropine or mercaptopurine was allowed if patients were on stable doses. Exclusionary criteria included patients with anemia, leukopenia, thrombocytopenia, pregnancy or breast feeding, ulcerative colitis, indeterminate colitis, ulcerative proctitis, bowel surgery within 6 months, resection of >
50cm of the ileum, ileostomy, colostomy, or septic complications. Also excluded were patients with gastrointestinal abscess, perforation, active draining fistulae considered clinically significant, perianal lesions, history of colorectal cancer or colorectal dysplasia, parenteral or tube feeding, and evidence of infectious colitis or other enteric pathogens at screening.\textsuperscript{14}

Randomization was provided by the drug packaging vendor and employed a software algorithm to allocate patients to the different cohorts based on study design. Dose suspensions were given in amber glass containers with black outer lacquer to conceal the contents from patients and researchers, thus preserving blinding. The gastrointestinal symptoms of helminth infection may closely resemble the intestinal manifestations of IBD. To help differentiate the source of symptoms, researchers performed comprehensive medical histories to establish a baseline in each patient before starting therapy. Overall characteristics of the two groups were similar; however, the mean age of the placebo group was 10 years older than the treatment group and there was some variation in the pre-treatment symptoms of each group. All patients completed the 14-day follow-up period. Five patients discontinued during the 6-month follow-up.\textsuperscript{14}

Analysis of TSO therapy including all of the combined doses illustrates TSO as generally well tolerated and associated with a relative risk reduction of 16.7%. In the initial 14-day follow-up period, 10/27 (37%) TSO patients (3 in TSO 500, 1 in TSO 2500 and 6 in TSO 7500) and 4/9 Placebo patients (44.4%) experienced TEAEs.\textsuperscript{14} The most commonly reported adverse events involved gastrointestinal complaints such as diarrhea, nausea, and vomiting. There was no evidence of a dose dependent relationship to these events. While the TSO 7500 had the highest incidence of TEAEs (66.7%), the TSO 2500 had a TAEAs event rate lower than both the placebo and TSO 500 groups (11.1%). In addition, the authors found no significant TAEAs and relatable
dose relationships during the six month follow-up. Upon study completion, there was no evidence of parasite or ova in any patient stool sample.\textsuperscript{14}

**Summers et al (2005) RCT**

This was a randomized, double-blind, placebo-controlled trial\textsuperscript{15} in which the primary outcomes were to determine the efficacy and safety of TSO therapy in patients with ulcerative colitis versus those receiving placebo therapy. The trial was conducted by the University of Iowa’s Center for Digestive Diseases and elected private practices in Iowa. The trial enrolled 54 adult patients, ages 18-72 years old with active colitis defined by an Ulcerative Colitis Disease Activity Index (UCDAI) score of at least four. The index is a tool used to assess the severity of disease in patients with ulcerative colitis. It has four components (stool frequency, rectal bleeding, mucosal appearance, and the physician’s rating of disease activity). The Simple Index, or Simple Clinical Colitis Disease Activity Index (SCCDAI) was used as a secondary index to evaluate disease activity through five criteria (day and night stool frequency, urgency of defecation, blood in the stool, general wellbeing, and extra colonic features).\textsuperscript{15}

Included patients were allowed to use concurrent UC anti-inflammatory oral medications such as sulfasalazine, mesalamine, prednisone, azathiprine, or 6-mercaptopurine as long as their dose and length of use fit within the study parameters. Inclusion also required an assessment of laboratory parameters such as complete blood count (CBC), anemia profile, and liver and kidney function. Female patients were required to use birth control and have a negative pregnancy test upon study entry. Patients were deemed ineligible for a UCDAI score <4, the presence of fulminant colitis, an expected blood transfusion need for GI bleed, or the presence of peritonitis. Additionally, patients were excluded if stools contained enteric pathogens or *Clostridium difficile*; received treatment in the past 12 weeks included cyclosporine, methotrexate, or
immunomodulatory agents other than azathoprine/6-MP; received treatment in the last 2 weeks included antibiotics, antifungal, or antiparasitic medications; there was the presence of active hepatitis C, cytomegalovirus, herpes simplex, or immunodeficiency virus; there was a history of cancer; other clinically significant diseases were present that could interfere with protocol compliance or interpretation of the results; or there was a history of chemical abuse.¹⁵

Fifty-four patients were randomized via a random set of numbers. Thirty patients received oral TSO 2500 and 24 received placebo at 2 week intervals for 12 weeks. A person not involved in the investigation performed randomization and preparation of the vials. The vials containing TSO and placebo were disguised with charcoal and phosphate buffered saline to maintain blinding. No patients were lost to follow-up, however, two were withdrawn due to protocol violation. Double-blinding was maintained until study completion. The baseline characteristics of the two study groups revealed no significant differences.¹⁵

The primary measure of efficacy was a reduction of the UCDAI score by 4 or more points. Clinical remission was a secondary endpoint, defined as UCDAI ≤ 2. Additionally, researchers evaluated safety by searching for any side effects or complications that could be attributed to the therapy, significant changes to baseline hematological or biochemical measures, including hepatic and renal profiles and presence of mature parasite or ova in stool.¹⁵

Patients were analyzed using intention to treat. TSO therapy for the treatment of ulcerative colitis showed a significant response (UCDAI reduction of ≥ 4 points) when compared to patients receiving placebo (43.4% vs. 16.7% respectively, RR=2.6, NNT=4). The mean UCDAI score went from 8.77 ± 0.35 to 6.1 ± 0.61 (p 0.0004) in the TSO group. The SCCDAI score of the TSO treatment group was also found to be significant at week 10 (p=0.0736) while placebo patients did not show significant change. Conversely, the number of patients achieving
clinical remission was not significant. Only 3/30 TSO patients and 1/24 placebo patients achieved a UCDAI between 0-1.\textsuperscript{15}

No adverse events were experienced that could be attributed to the TSO treatment. Also, there were no significant changes to the baseline hematological and biochemical markers. Finally, there was no evidence of \textit{Trichuris suis} identified in the stool samples of any patients.\textsuperscript{15}

The authors state that TSO therapy given every 2 weeks is effective to reduce the symptoms associated with UC. They also suggest that this treatment warrants further investigation. Studies with larger sample sizes and the use of different dosages may help broaden the understanding of TSO therapy.\textsuperscript{15}


This study\textsuperscript{16} is the first of two observational case series reports included in this review. Performed in 2005, this was a 24-week open label study investigating the safety and possible efficacy of TSO therapy in adult patients with diagnosed Crohn’s disease. Patients were recruited by the University of Iowa and eligible for study inclusion if their Crohn’s Disease Activity Index (CDAI) score was between 220 and 450, correlating with moderate disease activity. The CDAI is considered the gold standard of clinical trials for measuring the disease activity of patients with Crohn’s disease. Patients also continued use of concurrent Crohn’s medications like mesalamine or derivatives, oral prednisone, azathioprine, or 6-mercaptopurine if they had been using the medication for a specified period of time at stable dose. Laboratory measures including CBC, hepatic and renal profiles, and stool samples were examined for any abnormalities that would lead to exclusion. Further exclusionary criteria included history of ileostomy, colostomy, resection >50cm, obstructive symptoms, or anticipated need for surgery. Patients were also
excluded if recently treated with immunomodulatory agents, antibiotics, antifungal, or antiparasitic medications.¹⁶

Efficacy was investigated by measuring disease activity through the use of the CDAI. Significant response was defined as a decrease in the CDAI >100 points or if the CDAI dropped below 150. A CDAI score of 150 correlated with disease remission. Twenty-nine patients were recruited and ingested TSO 2500 every 3 weeks for a period of 24 weeks. Their mean CDAI score at entry was 294. No patients were lost to follow-up; however, five patients withdrew from the study before completion.¹⁶

Data analysis at 24 weeks demonstrated a significant response (drop in CDAI>100 points or CDAI <150) in 23/29 (79.3%) of involved patients. Also notable was the high rate of patients experiencing remission, with 21/29 (72.4%) achieving a CDAI score below 150. Of those patients that responded to therapy, the mean CDAI improvement was 187.2 points. None of the patients developed any adverse reactions or new symptoms during the study period. Laboratory data demonstrated no significant differences to baseline levels and there was no indication of parasite or ova in patient stool samples.¹⁶

The authors suggest that the results of this trial lend evidence to TSO as a well-tolerated and effective form of therapy for Crohn’s disease. However, they acknowledge the possibility of placebo effect due to the open label nature of this study. They also postulate the confounding effect of concurrent use of Crohn’s medications as their subset analysis did indicate that those patients had better outcomes compared with those not using concurrent immunosuppressive therapy. They recommend further clinical trials involving blinding and control groups.¹⁶

The last study reviewed was an observational open label case series report\textsuperscript{17} involving seven patients with IBD. The primary aim of this study was to investigate whether a single dose of TSO 2500 was safe for IBD patients and assess the effect of this therapy on disease activity and quality of life. Four patients with active CD and 3 patients with UC were enrolled and followed every 2 weeks for a total of 12 weeks. Eligible patients were at least 18 years of age and needed a diagnosis of UC or CD confirmed through colonoscopy or sigmoidoscopy. Female participants had to be non-pregnant and using contraceptives. Patients were allowed to continue concurrent medical therapy such as prednisone, antibiotics, 5-aminosalicylates, azathropine, or 6-mercaptopurine as long as the doses were stable for a designated length of time and the dosage was not changed during the study timeframe. Exclusionary criteria included patients with fulminant colitis or a CDAI <220, ileostomy or colostomy, bowel resection >100cm, or anticipated need for surgery. Patients were also excluded if they had concurrent systemic diseases, history of cancer, drug or alcohol abuse, or pathogens in stool samples. Due to the small number of patients in the study, the baseline characteristics of those included were quite varied.\textsuperscript{17}

Disease activity was monitored using the SCCAI, CDAI, and the Inflammatory Bowel Disease Quality of Life Index (IBDQ). Clinical remission correlated with a reduction in the CDAI to \( \leq 150 \) for patients with CD, an SCCAI score \( \leq 4 \) for UC patients and an increase in the IBDQ to \( >170 \) points for all patients. Safety was evaluated through baseline and regular monitoring of laboratory tests every 2 weeks. Of the seven that participated, six patients (three UC and three CD) achieved remission during the 12 weeks according to the above indices. On average, remission lasted 8 weeks for the abovementioned patients. One CD patient did not
achieve remission, yet her CDAI score did drop 153 points during treatment. During the 12 weeks study period, there was no report of adverse events that could be attributed to the study agent and baseline laboratory parameters did not significantly change. As a secondary endpoint, four of the patients in this study were also included in maintenance period testing to investigate the safety of repetitive doses after the initial 12-week study. They were each given TSO 2500 every 3 weeks for varying amounts of time. All of the patients included in the maintenance period dosing saw improvements to their disease activity. Of these 4 patients, 3 entered remission for a period longer than 1 year, indicating that multiple doses may prolong remission. The authors ascertain that no significant complications or adverse effects were caused from multiple doses of TSO 2500 during this period.

The authors concluded that although this study is greatly limited by sample size, lack of blinding, and control group, they are nonetheless encouraged by the improvement witnessed in this study. They support further exploration of TSO therapy using a larger double-blind, placebo-controlled study.

**DISCUSSION**

Crohn’s disease and ulcerative colitis are severe, debilitating, and chronic diseases associated with substantial clinical and economic costs. In the United States, the annual cost of treating IBD is estimated at $6.3 billion. Costs associated with missing time from work for individuals with IBD is also significant, amounting in $249 million each year. While there are medications available that aid in the symptomatic management of UC and CD, there are no cures. Standard therapies include systemic corticosteroids, locally acting steroids, aminosalicylates like 5-ASA and sulfasalazine, immunomodulators, methotrexate, and biologic therapies such as infliximab. Many of these therapies come with hefty price tags and the run risk of serious, even life-
threatening side effects. Furthermore, considerable portions of patients suffering from IBD are refractory to modern pharmaceutical therapies. There is a great need to explore safer, more effective, and less costly treatment options for patients with this condition.

With their ability to modulate the inflammatory responses of an overzealous immune system, helminths may be the answer in the search for more effective therapies. Collectively, the studies in this review all support the use of TSO in the treatment of IBD. The randomized, double-blinded, placebo-control clinical trial by Sandborn et al\textsuperscript{14} demonstrated no increase in complications or adverse events associated with increasing doses of TSO therapy in patients with Crohn’s disease. Although the study had good methodology, it is limited due to the use of a small sample size of 36 participants and inconsistency with the prognostic imbalance of pre-treatment symptoms and mean age. Individuals receiving TSO 7500 tended to exhibit slightly worse pre-treatment symptoms when compared with the other groups, while TSO 500 patients fared better in their pre-treatment symptoms severity.\textsuperscript{14} This inconsistency could help explain the high incidence of TEAEs within the TSO 7500 with 66.7\% of individuals experiencing symptoms. However, no dose response relationship was found based on the analysis showing that placebo had more events than both TSO 500 and TSO 2500. Overall, this study found that helminth therapy was associated with a decreased chance of having a TEAE when compared with placebo (RRR 16.7\%) and TSO 2500 had the least TEAEs of any dose.\textsuperscript{14}

A dose of TSO 2500 was also investigated by Summers et al (2005) RCT\textsuperscript{15} in their randomized, double-blind, placebo-controlled study. In addition to safety, they were primarily interested in the effectiveness of TSO therapy in patients with UC. Their results showed significant benefit in disease activity for those using TSO therapy compared with placebo in individuals with ulcerative colitis (RR 2.6, NNT\textsuperscript{=}4). This study had good methodology but had
some minor limitations. A shortcoming of this study was the lack of statistical significance for their secondary endpoint of clinical remission (UCDAI ≤ 2). The authors simply state that there were few remissions without listing further data for analysis. The study also has serious imprecision as the sample size is small. Overall, the results of this study somewhat support the efficacy of this non-traditional therapy.

Paving the way for the abovementioned randomized control trials, Summers and colleagues conducted smaller, observational case series reports\textsuperscript{16,17} to investigate the safety and tolerability of TSO 2500. These two studies were the first attempts to explore the use of TSO therapy in humans with IBD. Both studies are of very low quality due to small sample sizes and the fact that they were case series reports. In both studies there is a greater potential for placebo effect based on the idea that patients were aware they were receiving helminth therapy. In Summers et al (2005) case series,\textsuperscript{16} there was a significant improvement in the disease activity of patients with Crohn’s disease receiving TSO therapy with 79% of patients achieving a 100 point reduction in their CDAI or a score <150. Moreover, 72% of patients also achieved remission within the 24-week study period. In their 2003 pilot study,\textsuperscript{17} Summers et al also showed a significant response to TSO therapy with all patients experiencing significant reductions in the scales used to assess disease activity. Prior to TSO therapy, all of the patients selected for this study had been refractory to conventional medical therapy. Six of these seven patients achieved remission. These results strongly support the use of TSO therapy in IBD patients, especially in those that have been refractory to traditional pharmacological therapy.

In addition to efficacy, safety of TSO therapy is a very important outcome when considering use in humans. In many parts of the world, helminth infection is associated with significant morbidity. According to the World Health Organization,\textsuperscript{21} morbidity is related to the
number of worms harbored, with heavier infections causing a myriad of symptoms including abdominal pain, diarrhea, weakness, anemia, and impaired cognitive and physical development. All four of the studies included in this review demonstrated no statistical increase in adverse events or complications associated with TSO therapy. There was no worsening of standard laboratory data and no observable presence of ova or parasite found in any of the stool samples collected for investigation.\textsuperscript{14-17}

Currently, there are two large-scale clinical trials investigating the use of TSO for the treatment of Crohn’s disease. The purpose of the TRUST-1 study\textsuperscript{22} is to evaluate the safety and efficacy of TSO 7500 in a randomized, double-blinded, placebo-controlled 12-week trial. Researchers enrolled 250 individuals suffering from mild to moderate Crohn’s disease. The study is ongoing and preliminary results show that the study did not meet its primary endpoint of improving response or secondary endpoint achieving remission. The European TRUST-2 study\textsuperscript{23} is a multi-center randomized control trial to evaluate three different doses of TSO in patients with Crohn’s Disease. In late 2013, on the recommendation of an independent data monitoring company, this trial was terminated due to lack of efficacy.\textsuperscript{24} The primary endpoint of response and secondary endpoint of remission were not met. Since the information gained from these trials appears to conflict with the data supported by the four articles included in this review, only a weak recommendation can be made in using TSO therapy when addressing IBD symptoms.

**CONCLUSION**

Inflammatory bowel disease appears to result from a combination of genetic and environmental factors that generate an inappropriate immune response. Through complex interactions with their host’s immune system, helminths seem to down-regulate the inflammatory immune response. The hygiene hypothesis speculates that exposure to helminths could help
protect from the development of diseases like Crohn’s and ulcerative colitis. Epidemiologic data, animal studies, and the four human trials evaluated above demonstrate that TSO therapy may have a positive effect on disease activity, while also appearing safe for use in humans.

However, when considering the evidence, the overall quality of the combined articles is low. This is due to the inherent nature of observational studies as well as the small sample sizes used in each trial. Furthermore, the recent preliminary data released from larger phase two clinical trials suggests that TSO might not be the answer that many are hoping for. Nevertheless, the generous safety profile of this investigational drug and its use in patients refractory to traditional pharmacologic treatments warrants further exploration.
References


## Table I. Characteristics of Reviewed Studies, GRADE Profile

<table>
<thead>
<tr>
<th>Study Area</th>
<th>No. of Studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Inconsistency</th>
<th>Publication bias</th>
<th>Quality</th>
<th>Importance</th>
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<tbody>
<tr>
<td><strong>Reduction of Disease Activity</strong></td>
<td></td>
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<tr>
<td>3</td>
<td>1 RCT</td>
<td></td>
<td>Serious limitations&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No serious indirectness</td>
<td>Serious imprecision&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No serious inconsistencies&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No bias likely&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Low</td>
<td>Critical</td>
</tr>
<tr>
<td></td>
<td>2 Observational</td>
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<td></td>
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</tr>
<tr>
<td><strong>Remission</strong></td>
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<td></td>
<td></td>
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<tr>
<td>3</td>
<td>1 RCT</td>
<td></td>
<td>Serious limitations&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No serious indirectness</td>
<td>Serious imprecision&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Serious inconsistencies&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No bias likely&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Low</td>
<td>Critical</td>
</tr>
<tr>
<td></td>
<td>2 Observational</td>
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</tr>
<tr>
<td><strong>Adverse Drug Reactions of Complications Attributable to the Therapy</strong></td>
<td>4</td>
<td>2 RCT</td>
<td>Serious limitations&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No serious indirectness</td>
<td>Serious imprecision&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No serious inconsistencies&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No bias likely&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Low</td>
<td>Important</td>
</tr>
<tr>
<td></td>
<td>2 Observational</td>
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</tr>
<tr>
<td><strong>Significant Changes to Standard Laboratory Analysis of Hematological and Biological Markers</strong></td>
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<td>1 RCT</td>
<td>Serious limitations&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No serious indirectness</td>
<td>Serious imprecision&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No serious inconsistencies&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No bias likely&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Low</td>
<td>Important</td>
</tr>
<tr>
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</tr>
<tr>
<td><strong>Presence of Parasite or Ova in Stool Upon Study Completion</strong></td>
<td>3</td>
<td>2 RCT</td>
<td>Serious limitations&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No serious indirectness</td>
<td>Serious imprecision&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No serious inconsistencies&lt;sup&gt;a&lt;/sup&gt;</td>
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</table>

<sup>a</sup>Lack of prognostic balance at the beginning of the Sandborn et al trial<sup>14</sup> and both observational studies<sup>16,17</sup> did not have control populations

<sup>b</sup>Small sample sizes

<sup>c</sup>The Summers et al (2005) RCT<sup>18</sup> did not report data consistently
Table 2. Sandborn et al RCT\textsuperscript{14} Summary of Findings

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TSO 500</th>
<th>TSO 2500</th>
<th>TSO 7500</th>
<th>TSO total</th>
<th>Control Group</th>
<th>Relative Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAEs</td>
<td>3/9 (33.3%)</td>
<td>1/9 (11.1%)</td>
<td>6/9 (66.7%)</td>
<td>10/27 (37%)</td>
<td>4/9 (44.4%)</td>
<td>16.7</td>
</tr>
</tbody>
</table>

Table 3. Summers et al (2005) RCT\textsuperscript{15} Summary of Findings

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TSO 2500</th>
<th>Control Group</th>
<th>Relative Risk</th>
<th>NNT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy: (UCDAI decreases by ≥4)</td>
<td>13/30 (43.3%)</td>
<td>4/24 (16.6%)</td>
<td>2.6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Remission: (UCDAI ≤2) <strong>no numbers given, authors stated as insignificant</strong></td>
<td><strong>no numbers given, authors stated as insignificant</strong></td>
<td><strong>no numbers given, authors stated as insignificant</strong></td>
<td><strong>no numbers given, authors stated as insignificant</strong></td>
<td><strong>no numbers given, authors stated as insignificant</strong></td>
<td><strong>no numbers given, authors stated as insignificant</strong></td>
</tr>
<tr>
<td>UCDAI 0-1</td>
<td>10%</td>
<td>4%</td>
<td></td>
<td></td>
<td>Not significant</td>
</tr>
</tbody>
</table>

Table 4. Summers et al (2005) Case Series\textsuperscript{16} Summary of Findings

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TSO 2500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy: (CDAI decreases &gt; 100 points or CDAI score &lt;150)</td>
<td>23/29 (79.3%)</td>
</tr>
<tr>
<td>Remission: CDAI &lt;150</td>
<td>21/29 (72.4%)</td>
</tr>
</tbody>
</table>

Table 5. Summers et al (2003) Case Series\textsuperscript{17} Summary of Findings

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TSO 2500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission: IBDQ ≥170</td>
<td>6/7 (85.7%)</td>
</tr>
<tr>
<td>Remission: CDAI ≤150</td>
<td>3/4 (75%)</td>
</tr>
<tr>
<td>Remission: SCCAI ≤4</td>
<td>3/3 (100%)</td>
</tr>
</tbody>
</table>