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## HELMINTHIC THERAPY IN CROHN'S DISEASE: A REVIEW

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**Abstract:** The incidence of the Crohn's disease (CD), an inflammatory bowel disease is markedly increased in industrialized countries during the last decades. Different pharmacological agents are currently used in several combinations to control the inflammatory process, including helminthes. There is a lot of scientific data in animal models and human host that favors an immunoregulatory role of helminth infection in Crohn's Disease. Recently, the hygiene hypothesis of the development of immunological diseases was proposed, stating that raising children in extremely hygienic environments with less exposure to parasite infections may negatively affect the development of the immune system, predisposing them to immunologic diseases such as CD. Thus lack of exposure to parasites may critically contribute to the risk of CD. This hypothesis is supported by experimental data showing that helminthic parasites protect against T helper (TH) type 1 cell-mediated gastrointestinal inflammation in Crohn's disease. Both TH-2 cells and regulatory T-cells may be involved in this immunomodulatory mechanism. Helminth infection may activate goblet cells and mast cell which increases mucus and water secretion into the gut lumen. Adult worms live in the host small intestine for an average of five years. Infection can be easily terminated with an anthelmintic. No severe adverse effects have been reported thus far. Inoculation proved safe, even in immune suppressed patients. This review highlights the clinical use of helminthes like *Trichuris suis* and other for Crohn's disease (CD), a new perspective of therapy for CD.

**Keywords:** Inflammatory Bowel Disease, Crohn's Disease, Helminthic Therapy



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## INTRODUCTION

Crohn's disease (CD) an inflammatory bowel disease (IBD, is a chronic, relapsing, inflammatory disorder of the gastrointestinal tract. In the last decade, our understanding of the etiology and pathogenesis of Crohn's disease has improved considerably. Treatment of the disease includes conservative measures as well as surgical approaches in those who are non-responders to medical treatment. The primary therapeutic goals are related to improvement of patient quality of life by inducing and maintaining remission, predicting, preventing and treating complications, restoring nutritional deficits, providing appropriate psychosocial support, and modifying the course in those with aggressive disease. Pharmaceutical treatment of Crohn's disease includes five major categories, namely anti-inflammatory drugs, immunosuppressant's, biologic agents, antibiotics, and drugs for symptomatic relief. In recent years as a result of an increased knowledge of the underlying path physiology, several other treatment measures have been produced and studied including helminthes. These measures are designed to minimize the inflammatory process through inhibition of different targets.

### Helminths

Weinstocks *et al*<sup>[1]</sup> have proposed that, in our zeal to rid the intestines of parasites, we have eliminated a T cell regulatory mechanism that our immune system expects to be present. In Western countries modern hygienic practices prevent exposure to parasitic worms. The Inflammatory Bowel Disease hygiene hypothesis states that raising children in extremely hygienic environments impairs immune development, which predisposes them to immunological diseases such as IBD later in life.<sup>[2]</sup> Epidemiologic studies suggest that people harboring infection from helminths are affected by immune-mediated disease to a lesser degree. Helminthes are common in tropical climates and in populations subject to crowding and poor sanitation. Consequently, people living in less developed countries are probably protected from chroh's disease development. Helminth stimulates their host's immune regulatory circuitry by interacting with host innate and adoptive immunity, thus reducing aberrant inflammatory response. It seems therefore that exposure to helminths may help prevent or even ameliorate CD. Experimental data further supported this epidemiological assumption. Mice colonized with helminths are protected from the development of experimental colitis.<sup>[3]</sup> Animal models have confirmed a significant impact of helminth colonization on a variety of immune functioning, in particular, augmenting several immune regulatory cytokines, including interleukin 4 and 13, inducing regulatory T cells, and attenuating the TH1 type inflammatory response.<sup>[4-6]</sup>

### Rationale for the use of helminthes in Crohn's disease

A general consensus is that Crohn's disease is the result of the combined effects of 4 factors: environmental influences, genetic variations, intestinal microbiota alterations, and disturbances in the innate and adaptive immune responses. Probably, for the disease to be clinically expressed a combination of all these factors is necessary. However, it seems that each patient has a different combination of factors leading to the disease, explaining why each patient displays their own clinical picture and response to therapy.<sup>[7]</sup> Altered immune responses are considered to be quite important elements related to the pathogenesis of Crohn's disease. The innate immune system plays a significant role in the defense. Impairment of this system results in activation of the adaptive immune system leading to excessive proinflammatory cytokine production derived from CD4+ T cells over and above the response normally associated with tolerance and immunoregulation.<sup>[8]</sup> In CD the antigen presenting cells and macrophages produce mainly interleukin-12 (IL-12) and IL-18 resulting in a Th1-type polarization and production of pro-inflammatory cytokines including tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interferon- $\gamma$  (IFN- $\gamma$ ), and IL-2. Subsequently these cytokines stimulate the antigen presenting cells to secrete other cytokines including IL-1, IL-6, IL-8, IL-12, and IL-18, thus leading to a self-sustained cycle.<sup>[9]</sup> In response to helminthic infection the host mounts a mucosal response that includes Th2 cytokine production limiting helminthic colonization. Helminths and their eggs probably are the most potent stimulators of mucosal Th2 responses. Th2 cytokines mobilized in response to the helminth will prevent or antagonize the disease-promoting Th1 events in the gut. The Th2 response provoked by parasitic worms can modulate immune reactions to unrelated parasitic, bacterial, and viral infections. Perhaps failure to acquire these parasites and experience mucosal Th2 conditioning predisposes to Crohn's disease, which is an overly active Th1 inflammation.

### Mechanism of action of helminthes

Individuals having chronic helminthic infection rarely develop allergic or chronic autoimmune disease.<sup>[10]</sup> Because immunologically, intestinal worms seem to have three major effects on the immune system. First, helminthic infection opposes the Th1 response associated with autoimmune disease and CD by producing strong Th2 response.<sup>[11, 12, 13]</sup> Second, chronic infection with these organisms may generate a network of regulatory T (Treg) cells that secrete transforming growth factor TGF- $\beta$  and interleukin-10.<sup>[12,14]</sup> These cytokines may not only regulate aggressive Th1 responses but also control heightened Th2 responses that contribute to chronic allergic diseases. The data supporting these pathways come from both human and animal studies, with IL-10 levels elevated in chronic schistosome infection and reduced in patients with chronic allergic diseases from industrialised countries.<sup>[15,16]</sup> Data also indicate that helminth infection (*H polygyrus*) in the proximal small bowel is able to influence immunoregulatory cytokines downstream in the Peyer's patches of the terminal ileum.

Infection is associated with downregulation of IFN- $\gamma$ , upregulation of IL-4, IL-5, and IL-10, and a switch in lipopolysaccharide induced cytokine synthesis, from IL-12 to TGF- $\beta$ .<sup>[17, 18]</sup> Third, worms seem to alter the bacterial composition of intestinal flora. Research in mice suggests that helminths promote the growth of gut microorganisms typically considered to be 'probiotics', which help to maintain intestinal health. All of these experiments have the limitations of being carried out in the highly controlled environment in animal models, and some also involve a cell isolation step. No similar human data are available. However, experience has taught us that human IBD is not as simple as Th1 versus Th2<sup>[19]</sup> and therefore other "anticolitis" mechanisms of protection and repair may be in place during helminth infection.

### Other protective mechanisms

Helminthic infection may activate goblet cells and mast cell which increases mucus and water secretion into the gut lumen.<sup>[20, 21]</sup> This may influence the interaction between gut bacteria, their products, and a diseased epithelium, as well as impacting on intestinal motility. Helminth may also influence the microbial ecology of the gut<sup>[22]</sup> and the neuroendocrine response, with an increase in neurotransmitters such as vasoactive intestinal polypeptide.<sup>[23]</sup> None of these factors has been assessed in human studies.

### Clinical efficacy of helminthes

The most important studies on the safety and possible efficacy of the intestinal helminth *Trichuris Suis* in the treatment of patients with active CD are discussed below.

1. Efficacy of helminths in Crohn's disease Twenty-nine patients with active CD ingested 2500 live *T. suis* ova every 3 weeks for 24 weeks. At week 24, 79.3% responded and 72.4% remitted. Analysis at week 12 yielded similar results.<sup>[24]</sup>

2. Joel Weinstock and his colleagues at the University of Iowa are integral developers of this epidemiology. Weinstock treated seven patients that had ulcerative colitis and Crohn's Disease. Non-responsive to traditional therapy, they were then infected with pig whipworm (*Trichurus Suis*). The results of these phase I trials were remarkable. More than 70% of initial patients reported improvement. These findings launched a new field of intervention of polarized Th1/Th2 diseases called the low tech biologics. The principle was the use of whole organisms to treat diseases of autoimmunity, allergy and asthma. This breakthrough was licensed to Ovamed and later Biomonde.<sup>[25]</sup>

3. Hook worms are also being researched by a University of Nottingham researcher in England. In his tests, Dr. Pritchard found that his subjects showed lower amounts of inflammation in the intestines, which was measured by testing the T-cells of study participants. Those participating in the study also noticed that their allergy symptoms began disappearing. He soon became

known as the first helminthic therapy researcher to actually infect his subjects with hook worms.<sup>[26]</sup>

### Safety of therapeutic helminth infection

There are no adverse events thus far. Inoculation proved safe, even in immune suppressed patients adult worms live in the host small intestine for an average of five years. Infection can be easily terminated with an antihelminthic. Over time, hook worms can increase risk for anemia. Protein deficiency can also develop, leading to an impairment of mental functioning and stunting physical growth in some patients. Medications are available to offset these side effects, iron supplements may be prescribed if anemia is present.<sup>[26]</sup> Both human and animal studies indicate that a heavy helminth burden is associated with a greater immunoregulatory environment, while a light burden may be associated with an increased risk of allergic disease.<sup>[27]</sup> The current human trials in IBD patients use a transient infection and, despite this, demonstrate clinical efficacy and no significant allergic disease post-infection.<sup>[28]</sup> Long term data, particularly after repeated exposure, will provide further reassurance. Screening of patients for carriage of other potential pathogens before initiation of treatment may be required as there is evidence that coinfection with other known pathogens such as *Campylobacter jejuni* may result in serious infection, including septicemia.<sup>[29]</sup> A recent case report indicates that this coinfection and its serious consequences may also occur in patients.<sup>[30]</sup> Coinfection of *S mansoni* with *Toxoplasma gondii*, may also lead to a significant increase in circulating tumour necrosis factor  $\alpha$ , severe liver pathology, and death in a murine model.<sup>[31]</sup>

### Conclusion

Helminth therapy may provide us with a unique, safe, and efficacious alternative for CD management. Helminth could act as adjuvant for induction of T regulatory cells which inhibit the maturation of CD4 T cells to Th1 and Th2 effector cells, and reduce the occurrence of Th1-mediated diseases such as CD. Chronic helminth infestation provokes a state of chronic immune activation with anergy. Administration of ova of *T. Suis* has given encouraging results in the treatment of CD with a good safety record, but long-term trials are needed because of the potentially harmful effects of helminths on immunity. Other issues related to this that need to be addressed by future studies are the choice of organism and the type of infection. Controlled randomized studies will be further required to answer whether this form of treatment will be safe and effective for larger numbers of patients with Crohn's Disease. However, what these important and innovative studies demonstrate is the need for a greater understanding of the helminth-host relationship. This is slowly being addressed but almost exclusively in animal models. Identification of antigens or epitopes responsible for the generation of a tolerant environment is of special interest and one candidate is the schistosome oligosaccharide lacto-

N-neotetraose.<sup>[32]</sup> This molecule, which is also present in human milk, stimulates the expansion of a Gr1<sup>+</sup> cell population, which by increased production of IL-10 and TGF- $\beta$ , creates a Th2 biased immune environment and by directing naive CD4<sup>+</sup> T cells down the Th2 path. Molecules such as this may represent potentially novel therapeutic agents for chronic inflammatory disorders such as crohn's disease, and thus bypass the need for helminth inoculation and infection. Researches are continuing for advances in helminthic therapy to possibly develop less invasive ways of treating patients suffering from chroh's disease.

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