

The use of *Trichuris suis* and other helminth therapies to treat Crohn's disease

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Abstract Infections with gastrointestinal (GI) nematodes are prevalent worldwide, despite the fact that anti-helminthic medications are regarded as safe, efficient, and widely available globally. In this review, we highlight the potential therapeutic benefits that may be realized through the clinical use of *Trichuris suis* and other helminths for Crohn's disease (CD). Long-lived helminthic parasites are remarkable in their ability to down-regulate host immunity, protecting themselves from elimination, and also minimize severe pathological host changes. This review summarizes what is known about the underlying mechanisms that may account for the observed patterns in humans treated with helminths for CD. The Th2 arm of the immune system is emphasized as a component of primary importance in the association between the host immune system and GI nematode infections. Although GI nematode infections in humans cause significant morbidity and mortality, the existence and nature of protective mechanisms these helminths may confer remain largely unclear.

Introduction

Crohn's disease defined

Crohn's disease (CD) is a chronic autoimmune disease that can affect any area of the gastrointestinal (GI) tract, from the mouth to the anus, but most commonly affects the lower part of the small intestine, the ileum. The first published report of 'regional ileitis' or CD appeared in 1932 (Crohn et

al. 1932). Crohn's symptomatology can fluctuate greatly; it can cause a lifetime of trouble or remain relatively mild. Our review focuses on CD within the larger context of inflammatory bowel diseases (IBDs). Ulcerative colitis (UC) and CD are two of the more important IBDs, both of which are of unknown etiology. Approximately 2 million people in the USA and Europe have CD or UC, which usually begins during the second to third decade of life (Weinstock et al. 2004). The swelling associated with CD extends deep into the lining of the affected organ, can cause pain, and induce diarrhea; by comparison, UC usually affects only rectal and colonic mucosa. Although CD is restricted to humans, our review also examines selected experimental animal models that attempt to replicate the human condition. The biomedical community is gaining a better understanding of CD, particularly in regard to its genetic aspects, how the immune system malfunctions during the course of the disease, and mechanisms involved in the relationship between infection and chronic inflammatory disease. New drugs are currently being tested in clinical trials, some of which appear to provide greater relief of the symptoms with fewer adverse side effects (Egan and Sandborn 2005). Surgical techniques continue to be refined (Fearhead et al. 2006), and novel treatments continue to be explored including the use of helminth therapy. GI nematode infections in humans cause significant morbidity and mortality globally, yet the existence and nature of protective mechanisms against these parasites remain largely unclear (Garside et al. 2000; Zacccone et al. 2006).

Current therapeutic strategies aim to modify the inflammatory responses in affected individuals and strive to minimize injury to the intestines (Bebb and Scott 2004). IBDs can involve both the small and large intestines, and while pathologic findings are usually non-specific, they

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may suggest a particular type of IBD. The most common complication of CD is blockage of the intestine. Blockage occurs when the intestinal wall thickens in response to the disease resulting in swelling and scar tissue formation, resulting in stricture of the gut lumen. CD may also cause ulceration that may erode from the affected area into the urinary bladder, vagina, or skin. The areas around the anus and rectum are often involved, and fistulas are a common complication; fistulas may also become secondarily infected with bacteria. Although fistulas can sometimes be treated medically, many cases require surgical intervention.

Inflammation is typically transmural and can produce changes varying from small ulcers over a lymphoid follicle to deep fissure ulcers and transmural scarring with accompanied chronic inflammation. An extended period of inflammatory response is provoked by persistence of the causative tissue stimulus. One third of all reported human cases of CD have granulomas in both intestinal and in extra-intestinal sites such as lymph nodes, liver, and joints (Hanauer 1996). Inflammation is typically segmental with uninvolved intestinal areas separated from the afflicted areas; the inflammatory process is accompanied by simultaneous attempts at *healing and repair*. Helminths diminish immune responsiveness in naturally infected humans and reduce inflammation in colitis subjects experimentally infected with worms (Summers et al. 2005a). Infectious and immunologic mechanisms have both been proposed as potential etiologies (Weinstock et al. 2004); clinical manifestations are variable and can include extra-intestinal manifestations such as arthritis, uveitis, erythema nodosum, and ankylosing spondylitis. Researchers hope to study individuals who suffer from autoimmune conditions, such as rheumatoid arthritis and lupus, to see if a similar improvement in conditions can occur with helminth therapy as seen in CD (Simpson and Marshall 2004).

IBD “hygiene hypothesis”

Eradication of helminths through increased hygiene may be one change that has led to increased prevalence of certain diseases (Weinstock et al. 2004). The “hygiene hypothesis” (HH) for CD postulates that multiple childhood exposures to enteric pathogens protect an individual from developing CD later in life, whereas individuals raised in a more sanitary environment are more likely to develop CD (Yazdanbakhsh et al. 2002). In a broader context, the HH suggests that rising incidences of asthma, IBDs, multiple sclerosis, and other conditions may be, at least in part, the result of lifestyle and environmental changes (Weinstock 2006). Guarner et al. (2006) mentioned that helminths regulate their host’s immune system and prevent excessive inflammatory responses, which could underlie the mecha-

nism of “hygienic” protection. This hypothesis is supported by experimental data showing that helminthic parasites protect against T-helper (TH) type 1 cell-mediated GI inflammations like CD (Hunter and McKay 2004).

CD is common in industrialized developed countries where human helminth infections are relatively sparse; likewise, CD is uncommon in less developed areas of the world where many individuals harbor worms (Summers et al. 2005a,b). Elliott et al. (2000) noted that people in areas endemic for intestinal helminths are largely protected from IBD. Further, most of these people do not develop disease directly attributable to their intestinal helminths (Summers et al. 2005a). The immune system of these subjects seems adapted to helminthic colonization, and worms play a key role in preventing immune dysregulation in genetically susceptible individuals (Summers et al. 2005a,b). By eliminating relatively harmless organisms, an immunoregulatory imbalance may have inadvertently resulted, leaving individuals susceptible to autoimmune diseases like IBDs (Guarner et al. 2006).

However, the HH for CD is still controversial, and two Canadian case-control studies in the American Journal of Gastroenterology come to diametrically opposed conclusions; as of now, the certainty of the HH for CD is not confirmed (Lashner and Loftus 2006). The difference in the two studies may be partially related to variations in the study population (population based vs hospital based), age of onset, different genetic determinants, urban/rural residence (40% rural vs principally urban), or different exposures from the causative agent. There is an increased risk associated with family history, being Jewish, a smoking history, and a number of significant associations with CD and UC (on univariate and multivariate analysis), which support the HH (Bernstein et al. 2006). The authors suggest further exploration of this association in prospective studies. Guarner et al. (2006) considered how a reduced prevalence of organisms that have been part of human microecology for millennia (including saprophytic mycobacteria, bifidobacteria, lactobacilli, and helminths) and cause little, if any, harm to the host, might explain the increased prevalence of immune-mediated disorders in “westernized” countries. It is therefore reasonable that the human immune system may have been shaped by its relationship with parasitic worms, and this may be a necessary requirement for maintaining our immunological health (Zaccane et al. 2006).

Immunopathology of Crohn’s disease

The underlying immunological mechanism for this condition is still poorly understood and controversial despite recent data obtained from work in animal models, human

genetics, basic science, and clinical trials (Ehrhardt 1996; Sartor 2006). Key events in helminth immunopathology among the host cell population are dominance of the T-helper 2 cell (Th2) phenotype and the selective loss of effector activity, against a background of regulatory T cells, alternatively activated macrophages, and Th2-inducing dendritic cells (Garside et al. 2000; Maizels and Yazdanbakhsh 2003). It is also postulated that CD results from dysregulated T-helper (Th) 1-type mucosal inflammation (Elliott et al. 2003). Pronounced stimulation of the local B cell system is the major immunological alteration in CD, and a progressive deviation from the characteristic secretory IgA and IgM responses occurs in favor of local IgG production in association with increasing severity of the inflammatory process (Brandtzaeg 1985). Such an altered immunological homeostasis may contribute to the chronicity and relapse of the disease, but its possible involvement in the initiation of the lesion is largely unknown (Brandtzaeg 1985).

Animal models

Animals exposed to helminths are protected, to various degrees, from experimental colitis, encephalitis, and diabetes (Weinstock et al. 2005). Helminths can prevent and reverse intestinal inflammation in animal models of IBD (Elliott et al. 2005). Animal models have been useful in the identification of immune responses uniquely involved in IBD pathogenesis and in defining the vital roles of environmental influences, such as normal luminal bacterial flora and the genetic composition of the host, in modifying IBD-associated inflammation (Blumberg et al. 1999). Insights gained from animal models will be beneficial in the development of novel approaches to control CD-type inflammation, such as the use of anti-cytokine therapies and gene therapy, and the identification of genetic abnormalities and antigens driving chronic inflammation (Blumberg et al. 1999). Lamina propria mononuclear cells (LPMCs) from helminth-colonized mice make less interleukin (IL)-12 p40 and interferon (IFN)- γ , but more IL-4, IL-13, IL-10, transforming growth factor (TGF)- β , and PGE₂ compared to LPMC from naive mice (Weinstock et al. 2005). In addition, helminths can impede IL-12, IFN- γ , and tumor necrosis factor α release and promote IL-10, TGF- β , and regulatory T cell production (Elliott et al. 2005). IL-16 is a T lymphocyte-derived cytokine that uses CD4 as its receptor and therefore recruits CD4-bearing cells; however, the role of IL-16 in intestinal inflammation is unknown (Keates et al. 2000). Colonic mucosal IL-16 levels were elevated in CD, and anti-IL-16 monoclonal antibody reduced colonic injury and inflammation induced by trinitrobenzenesulfonic acid (TNBS) in mice, suggesting a

key role for IL-16 in the pathophysiology of IBD (Keates et al. 2000).

Immune-mediated resistance to infection in murine models is mediated by a T-helper 2-type immune response (Helmsby 2005). In most murine models, the inflammation is driven by both T-helper 1 (Th1) actions and by substances in the intestinal lumen (Weinstock et al. 2004). The hypothesis that parasitic infection may be beneficial in attenuating Th1-cell type inflammatory responses has been investigated (Helmsby 2005). Mice exposed to eggs of *Schistosoma mansoni* and then challenged rectally with TNBS to induce colitis demonstrated that schistosome egg exposure attenuated TNBS colitis and protected mice from lethal inflammation (Elliott et al. 2003). Systemic immune responses showed similar skewing toward Th2 and regulatory cytokine production in worm-colonized animal models and in humans (Weinstock et al. 2005).

A well-characterized inflammatory response caused by *Trichinella spiralis* has been studied to clarify the relationship between intestinal inflammation and the regulation of nitric oxide synthase-type 2 (NOS-2) expressions (Bian et al. 2001). A specific gut inflammatory reaction resulted in the inhibition of NOS-2 expression. This suggests that this down-regulatory mechanism could lead to the development of new strategies for the therapy for inflammatory conditions characterized by the over-production of nitric oxide. *T. spiralis* was also used in mice defective for cytokines to demonstrate that, although parasite expulsion is indeed IL-4 dependent, the enteropathy is also regulated by IL-4 (Garside et al. 2000). The IL-4-dependent protective response against the parasite operates by a mechanism other than merely the gross degradation of the parasite environment brought about by the immune enteropathy (Garside et al. 2000). However, the protective mechanisms involved in parasite expulsion are still unclear (Gupta 2005).

Induction of Th2 response

Eukaryotic pathogens are powerful selective forces for immune evolution (Maizels and Yazdanbakhsh 2003). Among the cells of the immune system involved in the pathogenesis of autoimmune disease, T cells have received the most attention, and several animal models of autoimmune diseases have provided the rationale for specific therapeutic targeting of T cell subsets, especially CD4 T cells (Hasler 2006). The reason for the long-standing association between intestinal pathology and protection against GI nematodes, and the apparent discrepancy between Th2-mediated protection and Th1-mediated pathology, can be rationalized through the role of IL-4 in these processes (Garside et al. 2000).

Immune responses that prevent infection with helminths

For chronic infection to occur, the parasite must first avoid clearance by the host immune system (Gupta 2005); helminths alter host mucosal and systemic immunity, inhibiting dysregulated inflammatory responses (Weinstock et al. 2005). For parasites of humans and animals that rely on vectors or on sexual contact for transmission, infection must not terminate before the occurrence of the crucial event that completes its life cycle (Gupta 2005). Multiple layers of immunoregulation have now been discovered in helminth infection; both cellular and complex molecular interactions are involved (Maizels and Yazdanbakhsh 2003). A form of parasitological immune evasion known as antigenic variation can assist in avoiding host recognition (Gupta 2005). Increased numbers of goblet cells (GC) and qualitative changes in mucus secretion have been noted subsequent to infection with a number of nematode parasites (Nawa et al. 1994). Mucin proteins may mediate this response by enveloping the parasites and/or interrupting luminal adhesion (Oswald 2006). However, the specific role of GC and mucus in the generation of a protective response vs its role in resolving intestinal inflammation after infection with GI nematode parasites remains largely unresolved (Garside et al. 2000).

Key events among the host cell population are dominance of the T-helper 2 cell (Th2) phenotype and the selective loss of effector activity, against a background of regulatory T cells, activated macrophages, and Th2-inducing dendritic cells (Maizels and Yazdanbakhsh 2003). Lipoxins play a key role in controlling potent pro-inflammatory responses triggered by infection with *Toxoplasma gondii* and *Mycobacterium tuberculosis* (Aliberti and Bafica 2005). To contain microbial dissemination, infected hosts must mount a powerful immune response to prevent mortality. Although many microparasites escape immune attack by antigenic variation or habitation in specialized niches, helminths appear to thrive in exposed extracellular locations, such as the lymphatics, bloodstream, or GI tract (Maizels and Yazdanbakhsh 2003).

The onset of the chronic phase of infection is characterized by continuous cell-mediated immunity and may be regulated by the lipoxins (Aliberti and Bafica 2005). Such immune-containment strategies have been reviewed from the host's perspective, to keep pro-inflammatory responses under control during chronic disease, as well as from the perspective of the pathogen, which pirates the host's lipoxygenase machinery to its own advantage for immune evasion (Aliberti and Bafica 2005). Parasites have evolved specific molecular strategies to induce the host landscape via immunomodulators released by helminths, including cytokine homologs, protease inhibitors, and other novel products implicated in immune suppression (Maizels and Yazdanbakhsh 2003).

Genetic influences

Whether inflammatory diseases arise as a result of genetic factors, shared causative triggers or as a consequence of other diseases or their resultant treatment, is largely unknown (Lovegrove 2005). CD affects men and women equally and seems to run in some families. About 20% of people with CD have a blood relative with some form of IBD, most often a brother or sister and sometimes a parent or child. Racial differences in IBD family history, disease location, and extra-intestinal manifestations exist, which underscore the need for further studies in minority populations (Nguyen et al. 2006).

Trichuris suis (pig whipworm) therapy

In clinical studies of patients with IBD, exposure to the helminth *Trichuris suis* reduces disease activity (Elliott et al. 2005; Summers et al. 2005a,b). *T. suis* is not a human parasite; its eggs are capable of colonizing a human host for several weeks and are eliminated thereafter without any specific therapy (Weinstock et al. 2005). Results from Summers et al. (2005a,b) support the hypothesis that helminthic exposure provides protection against some immune-mediated inflammatory disease such as CD. In the mentioned study, human helminthic parasites were considered as a therapeutic option, but many could not be used because there are no available sources other than a human carrier. Eggs from such a source would risk inadvertent transmission of pathogenic microbial agents; some human helminths may also have disease potential or raise public health concerns. Eggs shed in the stool are not capable of colonizing a host because they are not yet embryonated. *T. suis* cannot be cultured or raised in vitro but can be harvested from colonized pathogen-free pigs.

The possibility that intestinal helminths might protect their host from developing or maintaining IBD led the University of Iowa Health Care group to consider the use of *T. suis* in the treatment of active IBD. The ideal agent would colonize the intestine without invading the host. In addition, the source of the helminth needed to be pathogen-free to minimize the risk of co-transmitting other diseases that represent public health hazards, such as HIV or hepatitis B, C, or E; the porcine whipworm, *T. suis*, meets these requirements. Weinstock et al. (2005) studied 29 patients with long-standing CD refractory to standard treatments. Individuals were given repeated doses of the eggs of *T. suis*, prepared from pathogen-free animals. At week 24 of the trial, 21 were in remission, and another two were improved; these results were much better than any expected placebo response; none of the subjects had ill effects. The explanation may be that helminths blunt Th1

responses, which are known to be over-reactive in CD (Weinstock et al. 2005). In a separate open trial, researchers found that six of seven patients (86%) achieved remission within the IBD Quality of Life Index and also demonstrated improvement in the common clinical indices used to describe disease activity (Summers et al. 2005c). In an initial treatment and observation period, safety was monitored by following the patients' clinical status and laboratory studies at regular intervals, and a single dose of 2,500 live *T. suis* eggs was given orally; patients were followed every 2 weeks for 12 weeks while baseline medications were continued at the same dose throughout the study. To assess safety and efficacy with repetitive doses, researchers then gave two patients with CD and two with UC 2,500 eggs at 3-week intervals as maintenance treatment using the same evaluation parameters. The benefit was temporary in some patients with a single dose, but the authors suggest that symptom amelioration can be prolonged with maintenance therapy every 3 weeks. It is possible to down-regulate aberrant intestinal inflammation in humans with helminths, and the authors call for a controlled trial to better evaluate the results of *T. suis* therapy (Summers et al. 2005c).

Recently, 29 patients with active CD, defined by a CD activity index (CDAI) ≥ 220 , were enrolled in an open label study in which all patients ingested 2,500 live *T. suis* eggs every 3 weeks for 24 weeks, and disease activity was monitored by CDAI (Summers et al. 2005b). Remission was defined as a decrease in CDAI to less than 150, whereas a response was defined as a decrease in CDAI of greater than 100. At week 24, 23 patients (79.3%) responded (decrease in CDAI >100 points or CDAI <150) and 21 of 29 (72.4%) remitted (CDAI <150 ; Summers et al. 2005b). Mean CDAI of responders decreased 177.1 points below baseline, and analysis at week 12 yielded similar results while there were no adverse events. These results support the argument that helminths induce regulatory circuits that could prevent and treat IBD (Elliott et al. 2005).

Other helminth therapies

To test the hypothesis that parasitic infection may be beneficial in attenuating Th1-cell type inflammatory responses, Elliott et al. (2003) exposed mice to eggs of *S. mansoni* and then challenged the hosts rectally with TNBS to induce colitis. Elliott et al. (2003) found that the schistosome egg exposure attenuated TNBS colitis and protected mice from lethal inflammation. Systemic immune responses showed similar skewing toward Th2 and regulatory cytokine production in worm-colonized animal models and humans (Maizels and Yazdanbakhsh 2003).

Trichinosis in animals and humans often occurs after the ingestion of infective larvae in raw or undercooked meat. A

specific gut inflammatory reaction results in inhibition of NOS-2 expression, and the authors suggested that this down-regulatory mechanism could lead to the development of new strategies for the therapy for inflammatory conditions characterized by the overproduction of NO (Bian et al. 2001). *T. spiralis* was also used in mice defective for cytokines to demonstrate that, although parasite expulsion is indeed IL-4 (a key regulator in humoral-mediated and adaptive immunity) dependent, contrary to expectations, the enteropathy is also regulated by IL-4 (Garside et al. 2000). Despite experiments with TNF-R1-deficient mice showing that severe IL-4-regulated enteropathy is not required for immune expulsion of *T. spiralis*, it is still conceivable that Th2 cytokines are acting in a direct fashion to create an environment unfavorable for intestinal parasites (Garside et al. 2000). However, it remains to be directly shown whether these effects are sufficient to expel parasites.

Human parasitic worms (e.g., *S. mansoni*) can result in reduced airway inflammation in response to a model allergen suggesting a potentially broader human immune application (Mangan et al. 2006). In animal models, intestinal bacteria drive colitis, and in humans, certain alleles of the lipopolysaccharide (LPS) receptor protein Toll-like receptor 4 (TLR4) increase IBD susceptibility (Ince et al. 2006). Relative information is also available regarding Chagas disease, an insect-transmitted protozoan common in South and Central America, caused by *Trypanosoma cruzi*. Chronic lesions in chagasic megaesophagus from *T. cruzi* infection might be a consequence of immune-mediated mechanisms that last until the chronic phase of infection, and are dependent on the persistence of the protozoan in the host's tissue (Kirchhoff 1993).

The influence of the intestinal nematode *Heligmosomoides polygyrus* colonization on liposaccharide-induced LPMC cytokine responses in mice has been studied to understand helminthic immune modulation in the gut (Ince et al. 2006). *H. polygyrus* is a naturally occurring murine intestinal nematode that induces an immune response, causes phenotypic plasticity in metabolism and in organ structure and function, and results in changes in host reproductive output in mice (Kristan 2002). Thus, during helminth infection, LPS challenge induces mucosal T cells to make TGF- β through a TLR4-dependent process without promoting synthesis of pro-inflammatory cytokines (Ince et al. 2006).

Current understanding of helminth-protective mechanisms

The concept of a therapeutic effect from a parasite may appear paradoxical, but it is not new and is logical if one accepts that while exploiting the host, the parasite would benefit by providing some advantage to the host over non-infected

individuals (Desowitz 1981). Allergic inflammation does not appear to induce intestinal helminth expulsion but may reflect the extreme activation of the immune system in the gut in response to a complex pathogen (Garside et al. 2000). Elevations of anti-inflammatory and immunosuppressive cytokines (such as IL-10) that occur during long-term helminth infections are inversely correlated with allergy (Yazdanbakhsh et al. 2002). In the case of CD, which is associated with T-helper 1 (Th1) events, it is proposed that infection with parasitic helminths would be beneficial, where Th2 cytokines mobilized in response to the helminth will prevent or antagonize the disease-promoting Th1 events in the gut (Hunter and McKay 2004). However, although immune expulsion of GI helminth parasites is usually associated with Th2 responses, the effector mechanisms directly responsible for parasite loss have not been elucidated. Intestinal pathology observed in many other disease models closely resembles that seen in helminth infections, but has been attributed to Th1 cytokines (Garside et al. 2000).

However, because the pathogen causing IBD is still unknown, the HH of the development of immunological diseases was proposed; 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 IBD (Moreels and Pelckmans 2005).

Areas of future research

Eggs from a human helminthic source would risk inadvertent transmission of pathogenic microbial agents, and some human helminths have disease potential or raise public health concerns, which limit large-scale studies (Elliott et al. 2005). GI nematodes are powerful modulators of the immune response, and as such, they may have the potential to affect the outcome of concurrent infections with other parasites, bacteria, or viruses. They also appear to have the ability to influence the development of allergic reactions and modulate the effects of vaccination (Helmby 2005). If harboring helminths protects against immune-mediated disease, then these animals must be viewed as useful animals that may produce important compounds helpful for therapy for human disease (Elliott et al. 2005). Thus, future studies using helminth material, eggs, and larvae are warranted in studies to alleviate IBDs.

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