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REVIEW ARTICLE

Potential treatment of inflammatory bowel disease: a review of helminths therapy

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ABSTRACT

An inflammatory bowel disease (IBD) is most common in highly industrialized Western countries but uncommon in less developed areas of the world where helminths are frequent. The hygiene hypothesis proposes that the recent increase in allergic and autoimmune diseases is due to modern highly hygienic life styles and medical conditions. Loss of routine exposure to parasitic helminths, as a result of increasing lifestyle-associated factors, may be one factor leading to the increased disease prevalence.

In animal models and clinical trials of IBD, gastrointestinal nematodes colonization suppresses intestinal inflammation through multiple mechanisms including induction of innate and adaptive regulatory circuits. Studies using helminths like *Trichuris suis* or *Necator americanus* showed that these helminths are safe and may be effective therapeutic approaches for the control of IBD and other immune diseases. The aim of present review was to exploring the therapeutic use of helminths for the control of IBD.

Keywords:Inflammatory bowel disease, Helminthes, Therapeutic.

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Introduction

Inflammatory bowel disease (IBD) is a chronic intestinal disease that often has its onset during young adulthood and has a chronic relapsing-remitting course (1-3). The pathogenesis of IBD still remains incompletely understood but the complex of diverse genetic, environmental, ethnic variations and immunologic factors that share similar clinical manifestations and primarily affect the small intestine and colon. Definite causes of this disease remain unknown; however, IBD manifests from loss of immune tolerance to normal commensal enteric flora (4-6). The patients frequently experience continuous or intermittent diarrhoea, abdominal pain, rectal bleeding and fatigue due to aberrant intestinal inflammation probably resulting from inappropriately vigorous immune responses to components of our natural intestinal faecal stream (7).

For lack of a thorough understanding of the causes of IBD, the condition is categorized as either ulcerative colitis (UC) or Crohn's disease based on the location and duration of the inflammation, the microscopic pathology and the lack of

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identifiable inciting factors such as infection with enteric pathogens (8). The two diseases are basically different in that CD is usually a transmural inflammation, involving the whole thickness of the bowel wall, while UC is usually confined to the mucosa (9,10).

The prevalence of IBD and other autoimmune and inflammatory disorders is increased in industrialized nations in comparison to developing countries. The hygiene hypothesis was initially proposed by Strachan in 1989 for hay fever (3) and additional epidemiological studies were performed to further investigate the link between this hygiene concept and the incidence of other immunological diseases (11,12). Hygiene hypothesis suggested that the lack of exposure to infectious agents like helminths, as a result of improved living standards and medical conditions, modulates the development of the immune system and thereby increases the risk of inflammatory and autoimmune disorders (12-14).

The hygiene hypothesis is now proposed for several immunological disorders such as asthma and allergic diseases (11), diabetes mellitus Type 1, cardiovascular diseases, multiple sclerosis and IBD (12, 15-18).

IBD is more common in the industrialized world and the west, but it is increasing in other parts of the world as well. Northern Europe and North America have the highest IBD incidence rates whereas Crohn's disease and ulcerative colitis remain scarce in South America, Africa, and Asia (12, 19, 20**)**.

In Asia, for example, incidence rates still remain low as compared to Europe, but they have rapidly increased during the last three decades (21). Changing lifestyle is thought to be the major cause of the disease increase in low-incidence areas (12, 22).The range of the reported annual incidence of UC is 0.6–24.3 per 100,000 person-years in Europe, 0.1–6.3 per 100,000 person-years in Asia and the Middle East and 23.67 in Australia, 0–19.2 per 100,000 person-years in North America. The annual incidence range of CD is 0.3–12.7 per 100,000 person-years in Europe, 0.04–5.0 person-years in Asia and the Middle East and 0–20.2 per 100,000 person-years in North America (21).

China had the highest incidence of IBD in Asia (3.44 per 100,000 persons). The ratios of UC to CD were 2.0 in Asia and 0.5 in Australia. Complicated CD (stricturing, penetrating, or perianal disease) was common in Asia than Australia, and a family history of IBD was less common in Asia (23).

Helminth infections are exceedingly strong inducers of immune regulatory circuits (24, 25). The absence of such parasitic infections during childhood, are an important cause for the increased prevalence of IBD (24).

Thus infections seem to activate an important protective factor against these disorders (19). Identifying the nature of this protective effect and implementing this notion in therapeutic strategies against IBD (12).

The loss of helminthic infections was particularly important due to their especially strong stimulatory influence on host immune regulatory circuits. Animal experimentation as well as clinical and epidemiological studies supports this theory (26, 27).

In developed countries, parasitic worm infections are efficiently controlled by antihelminthic drugs and hygiene practices, and their eradication coincides with an increase in the development of immune disorders, including IBD (28).

Variations in more than 100-160 distinct genes can either increase or decrease the risk of acquiring either UC or Crohn's disease (8, 29, 30). IBD-associated polymorphisms affect pro-inflammatory and regulatory cytokines (such as IL10, TNFα and IFNγ), their receptors (such as IL1R2 and IL23R) as well as signaling pathways (e.g., SMAD3) and antigen presentation molecules or epithelial innate defense factors (32-34).

The intestinal bacteria can be altered by environmental factors, such as concentrated milk

fats or oral medications such as antibiotics. The entral microbiota is central for the initiation of IBD development. Bacteria (Pathogenic or commensal) trigger microbial sensing systems, which initiate pro inflammatory responses by innate cells, such as macrophages, dendritic cells producing interleukin (IL-12/23), TNF-α, IL-6, IL-1β. The following activation of the adaptive immune system leads to the strong production of inflammatory cytokines (IFN-γ, TNF-α, and IL-17A) by T helper cells, which constitute the dominant force driving chronic inflammation in IBD patients (35).

Experimental infections with helminthes or treatment with immunomodulatory worm-derived components has shown that helminths can efficiently suppress unrelated immune reactivity, including colitis. While current anti-inflammatory and immunosuppressive IBD therapies may induce and maintain remission, not all patients respond to such therapies and no long-term curative drug therapy has been developed to date. Studies in mouse models and human trials with IBD patients showing preventive and therapeutic effects of helminths have generated substantial interest (34).

Helminthic therapy consists of the inoculation of the patient with specific parasitic intestinal helminths. There are currently some related treatments available which include inoculation with *Necator americanus* (36) or *Trichuris suis*,*Trichuris muris* ova or larvae (37-41), or inoculation with *Trichuris trichiura* ova (42), *Heligmosomoides polygyrus bakeri* (41).

Exposure with this helminths prevents or reverses the Th1/Th17-type colitis of IL10 deficient (IL10-/-) mice (28,43). In trinitrobenzene sulfonic acid (TNBS) or Dextran Sodium Sulfate (DSS)-induced colitis, animals receiving intestinal helminths like *Trichuris suis*, *Trichuris muris*, *Heligmosomoides polygyrus bakeri*, *Trichinella spiralis*, *Hymenolepis diminuta* (44) or that receive non-viable *schistosome* ova, are protected from IBD. The mechanisms through which helminths function to alleviate disease remain incompletely understood (28, 41, 43-46)

Helminths, via their interaction with the host, activate several distinct immune regulatory pathways. This unique property of these organisms could render them highly effective at controlling IBD and other immune regulatory diseases (8).

Helminths modulation of IBD

Because TH1-mediated immune responses characterize the inflammatory infiltrate of both Crohn's disease and ulcerative colitis, at least partially, helminthes may exert their anti-inflammatory effect through the induction of specific TH2 cytokines (47,48).

Live helminths and their products have been shown to modulate a plethora of innate and adaptive immune cells (34). Nematode infections enhance the induction of dendritic cells supporting the outgrowth of regulatory T cell populations and production of anti-inflammatory IL10 in the intestine and gut-draining lymph nodes (34, 49). Macrophages are a target of nematode modulation, acquiring a regulatory phenotype (50-52). It is well appreciated that helminths promote the growth of IL4-producing, Th2 cells. Several investigations showed that abrogation of Th2 function promoted both Th1 cell differentiation and persistence of IBD in murine models of colitis, supporting the notion of the importance of worm-induced Th2 cytokines for disease control (34).

Multiple studies (39, 53, 54) have revealed that helminth-induced Th2 responses can attenuate damaging Th1-driven inflammatory responses in the host. A third lineage of effector CD4+ cells has been characterized by the production of IL- 17, the Th17 cell (12,55).

The biological actions of IL-17 are quite pro-inflammatory in character. It increases the local production of chemokines (such as IL-6, G-CSF,

GM-CSF, IL-1β, TGF-β, TNF-α), chemokines (including IL-8, GRO-α, and MCP-1), and prostaglandins (e.g., PGE2) from many cell types (keratinocytes, and fibroblasts, macrophages endothelial cells, epithelial cells) (54-57). Furthermore, it has been shown that IL-23 supports the proliferation of Th17 cells. IL-23 is mainly produced by macrophages and dendritic cells.

In addition to stimulating a vigorous Th2 response, helminth infections are also capable of inducing suppressive T cell populations known as regulatory T cells (Tregs) (54,58), which may help control morbidity and dampen resistance to re-infection through their potent immune regulatory mechanisms (54).

Regulatory cells express markers such as Foxp3, CD25, CTLA-4, LAG-3, CD127 GITR, and often secrete IL-10 and/or TGF-β (54, 59, 60). The number of Treg cells increases in the MLNs and the intestinal lining during helminthic infection. Lamina propria T cells make more IL10 and TGFb after *H. polygyrus bakeri* infection (8,61).

Tregs have been shown to play an important role in regulating immune responses and maintaining homeostasis under various disease conditions including cancer, autoimmune and inflammatory disease. Treg cells, which inhibit immune responses through cell-cell contact and through the production of immunosuppressive cytokines, type 1 Tr (Tr1) cells which secrete high levels of IL-10 and type 3 T (Th3) cells which primarily secrete TGF-β (12,62).

The combined induction of both TH2 and Tr1 cells may explain why the experimental treatment with parasite eggs has beneficial effects in both patients with Crohn's disease and in those with ulcerative colitis (48).

Experimental and clinical studies supporting helminth-based therapy

In the preliminary studies Elliott et al. proposed the hypothesis that the loss of exposure to parasitic worms increased the risk of IBD (28, 63).

Laboratories have developed several murine models of IBD that simulate the human condition. Animal models support this concept by showing that helminths can prevent IBD onset and reverse developed disease.

Reardon et al. showed that infection of mice with the tapeworm *Hymenolepis* ameliorated DSS - induced colitis (44). Khan et al. demonstrated that infection with *Trichinella spiralis*, protected mice from colitis induced by dinitrobenzenesulphate (DNBS) (45).

Elliott et al illustrated that *Schistosoma* egg exposure attenuated TNBS colitis and protected mice from lethal inflammation (46).

Schistosome egg exposure diminished IFNγ and enhanced IL-4 production from CD3-stimulated spleen and mesenteric lymph node cells and increased IL-10 mRNA expression in TNBS-treated mice (46).

IL-4 reduces IL-17A mRNA and blocked IL-17A secretion by T cells from colitic IL-10−/− mice, showing that nematode-driven Th2 effector cytokines effectively suppress pro-inflammatory responses (64).

Setiawan et al. showed that mice with *Heligmosomoides polygyrus* were resistant to TNBS-induced or piroxicam-triggered colitis, a Th1 cytokine-dependent inflammation. *H. polygyrus bakeri* colonization inhibits Th1 and promotes Th2 and altered LPMC cytokine profiles, blocking IFN-γ and IL-12 p40 release but promoting IL-4, IL-5, IL-13 (61).

Hang and Setiawan illustrated that In the Rag IL10−/− T cell transfer model of colitis, *Heligmosomoides polygyrus*, prevents and reverses intestinal inflammation. (43, 61, 65, 66).

Similar response patterns could account for the clinical improvement seen in inflammatory bowel disease with helminthic therapy (65).

Infections with *T. muris* lead to a pathological response resembling colitis in IL-10−/− mice, which were found to express high levels of IL-13Rα2 following T. muris infection. The authors

found that in IL-10/IL-13Rα2 double knockout mice, a subsequent increase in IL-13 bioactivity protected against IFN-γ and IL-17A-mediated colitis (40).

Based on the promising findings of helminth infections on experimental colitis, clinical studies were initiated. Treatment of patients with the porcine whipworm, Trichuris suis. When Elliott, Summers, and Weinstock initiated the first clinical studies with eggs of *T.suis* in the early 2000s, they reasoned that cases of IBDs were concentrated in the Western and industrialized world and rare in developing countries and that restoration of a less sanitized environment in the gut could be beneficial to patients with IBDs, as proposed by the hygiene hypothesis (64). *T.suis* is well tolerated and appears efficacious for Crohn's and ulcerative colitis in this open label trial (38,39). In the same line, Croese showed clinical efficacy of experimental infection with the human hookworm *Necator americanus* on Crohn's disease (36).

Conclusion

In developing countries, exposure to helminth infections and other pathogens are quite common. Recent evidence indicates that in hygienic industrialized countries, loss of exposure to helminths may be a predisposing factor for the development of IBD. Patients with IBD and other serious immune related diseases face a life-long struggle with these conditions. Most of the currently available therapies expose patients to substantial risk, while in many cases they provide limited efficacy. The risk from therapeutic helminthic exposure seems modest compared with the dangers of modern day therapies for IBD, which are well known to promote and worsen infections with other pathogens. Helminths influence innate as well as adaptive immune responses and this knowledge can contribute to new therapeutic approaches of helminth-induced protection.

The first step for considering parasitic helminths as a therapeutic option in IBD is the modulation of the Th1–Th2 cytokine balance, decrease in pro-inflammatory Th1 and Th17 responses and increase in anti-inflammatory Treg and innate regulatory cell responses, and protection from intestinal inflammation. Identification and characterization of helminth derived immunosuppressive molecules that contribute to the protective effect is necessary to avoid the possible disadvantages of a treatment with living parasites.

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