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Abbreviations

IBD: Inflammatory Bowel Diseases; TSO: Trichuris Suis Ova; UC: Ulcerative Colitis; CD: Crohn's Disease

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Mini Review

A Mini Review on Administrations of *Trichuris Suis* Ova as Therapy for Inflammatory Bowel Diseases

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Abstract

Crohn's disease and ulcerative colitis are two Inflammatory Bowel Diseases (IBD). They are marked by an abnormal response by the body's immune system. Some of the response may be attributed to genetic predisposition, while environmental factors play a role as well. It has also been noted that in people in developing countries that have been exposed to helminths have a lower prevalence compared to people not exposed to helminths in industrialized countries. This may be due to the augmented immunological response to antigens that comes with the helminth exposure. Studies have been conducted to determine the safety and efficacy of intestinal helminth, *Trichuris Suis* Ova (TSO) as IBD therapy. The results are promising for TSO therapy as treatment for IBD, but further investigation is warranted to better substantiate the findings.

Introduction

Ulcerative Colitis (UC) and Crohn's Disease (CD) are two major types of Inflammatory Bowel Diseases (IBD), which is a group disorders that involve chronic inflammation of the gastrointestinal tract [1], and both genetic and environmental factors play a part in the development of UC and CD. Approximately 18.8% and 50% of UC and CD, respectively, are genetically influenced [2]. Environmental factors, such as smoking and helminth exposure, have been attributed to the risk of developing IBD [3]. The pathogenesis behind IBD is not completely understood. It is known that with IBD, there is an abnormal immune response to environmental triggers. This immune response involves an aberrant mucosal infiltration of effector macrophages, neutrophils, and T cells, where they are activated and produce proinflammatory cytokines [4]. It is either this accumulation in effector T cell activation and/or modification of the immunological tolerance in T cells that seem to be responsible for the IBD.

For years, 5-Aminosalicyclic Acid (5-ASA), corticosteroids, biologics, and immunomodulators were used in treating IBD. The goal of these treatments was to reduce intestinal inflammation, thus enhancing the quality of life of those inflicted with IBD [5]. It had also been shown that IBD was less common in developing countries where there is a higher rate of helminthic colonization versus industrialized countries where this colonization is rare and uncommon [6]. This may have been due to the immune system inappropriately responding to gut microbiota [7]. Helminths down-modulate hyperactive immune responses [8,9], and this may be beneficial in CD and UC. Helminths have provided protection from colonic inflammation in experimental murine colitis [6]. *Trichuris suis* is a porcine whipworm that is like the human whipworm, *Trichuris trichiura*. It has been shown that the ingestion of the ova of *Trichuris suis* can lead to a self-limited colonization for a short period of time [10] and clinical improvement in patients with CD and UC.

Ulcerative Colitis Study

In an active ulcerative colitis study, patients were administered *Trichuris suis* (2500 ova in a final volume of 0.8 ml of phosphate-buffered saline [PBS] with 375 µg/ml charcoal) or a placebo (0.8 ml of PBS with 375 µg/ml charcoal) biweekly for a course of 12 weeks. The induction rates of clinical response and clinical remission were 13/30 (43.4%) and 3/30 (10%) for the ova treatment compared with 4/24 (16.7%) and 1/24 (4.17%) with placebo [7]. Adverse events were reported in 1/30 (3.33%) of ova treatment versus 4/34 (11.8%) of the placebo [7].

Crohn's Disease Study

Patients randomly received six biweekly suspensions of either 250, 2500, or 7500 *Trichuris suis* ova in 15 ml/day, or a 15 ml placebo solution/day, with four weeks' follow-up, in a double-blind, active Crohn's disease study [11]. The induction rates of clinical response were 16/39 (41%), 31/71 (43.7%), and 36/72 (50%) for the ova treatment, and 32/70 (45.7%) for the control. The clinical remission rates were 15/39 (38.5%), 25/71 (35.2%), and 34/72 (47.2%) for the ova treatment, and 30/70 (42.9%) for the placebo. Adverse events were mentioned in 28/39 (71.8%), 51/71 (71.8%), and 54/72 (75%) for the ova treated patients, and 51/70 (72.9%) in the control [11].

Discussion

Safe and efficacious ways to manage IBD have been and continued to be investigated. The premise of helminth exposure causing protection against IBD yielded studies with testing a helminth-based therapy. To combat IBD, human helminthic parasites were considered as an option for therapy. This option would be limited since a human carrier is required to be the source. Obtaining eggs from this source could lead to inadvertent transmission of the pathogenic microbes, which could culminate in disease potential and increase public health concerns. This led to investigating other options such as *Trichuris suis* as a helminth for the colonization, thus therapy. *Trichuris suis* is a parasitic helminth. The ova of Trichuris mature in the soil and are ingested. They hatch in the duodenum, and the subsequent larvae mature to adults in 6-8 weeks [7]. They localize to the terminal ileum and colon without invading the host [7]. These worms can be viable for 1-2 years. Mature adults produce ova that pass in the stool. Ova are not infective until they incubate for weeks for embryonation. Pigs are the natural host for *Trichuris suis*, but it can temporarily colonize humans without producing disease [10]. The human whipworm, *Trichuris trichiura*, and the porcine whipworm, *Trichuris suis*, are genetically similar. This may provide an explanation of the brief colonization.

The IBD result from abnormal immune response to intestinal flora based on genetic susceptibility, and this disrupts the balance between Th1-like and Th2-like cytokines [1]. Helminth colonization alters some modulatory pathways that regulate Th1-type inflammation [7]. Helminths stimulate the production of Th2 cytokines, interleukin 4 and interleukin 13, and this immune response blocks the production of Th1 cytokines, thus decreasing colitis severity [12]. Helminths also stimulate regulatory T cells and other inhibitory cytokines such as interleukin 10 and transforming growth factor β that play roles in mucosal homeostasis [13]. Previous works of TSO therapy may have limited its understanding. Some of the previous studies included small sample sizes of patients. Future studies should encompass a larger sample size. This could improve the power of a statistical test [1] used for analyzing the effects of TSO. Prior studies had a duration that may have been too short. These early exploratory studies, known as pilot and feasibility studies, are not definitive, and they serve to assess initial safety and determine whether there is sufficient promising activity to warrant larger follow-up studies [14]. Studies included 12 weeks as duration, and this period is typically used for testing pharmaceutical products. This time may not be the best fit for assessing a natural therapeutic, in which benefits may not materialize for at least 12 weeks. Also, like autoimmune diseases, IBD may consist of a long subclinical course and multiple epigenetic mechanisms to pathogenesis. It is possible that a longer helminth treatment period may need to be undertaken to adequately test the nematode's effect [14].

Also, besides the eggs, regulation of the host's immune response may be attributed to other excreted/secreted products of the porcine whipworm. Helminths and their excreted/secreted products are heavily glycosylated, and this reaction consists of typical helminth glycans and host-like glycans [15]. The presence of these glycans is important for helminths modulating the immune response in the host. The host-like glycans can affect dendritic cell maturation [15], and glycans have been shown to induce Th2 responses [16].

Conclusion

From previous studies, it has been found that the efficacy in TSO-treated patients with UC is high, and that their adverse events were lower. However, statistical significance was absent. *Trichuris suis* seems to be efficacious and well tolerated for CD, but clinically relevant effects were not that greater than the placebo. This therapy does seem to provide a new immunopathology for the prevention or even amelioration of IBD. It is also relatively easy to use, and this offers another advantage. If factors such as study duration and sample size of TSO are addressed, then there may be more statistical significance in the findings and more refinement in the therapeutical role of this helminth with these diseases.

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