Editorial

Whipping Crohn’s With Helminth Therapies? Not Yet

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The complex pathogenesis of inflammatory bowel disease [IBD] remains largely unknown. Current theories support the hypothesis that IBD is a multifactorial disorder that results from an abnormal immune response to commensal and/or pathogenic gut microbes in a genetically susceptible host. Environmental factors are thought to trigger the onset or reactivation of the disease.

Accumulating data show that the microbiota plays a crucial role in the onset and perpetuation of IBD. Genetic evidence revealed susceptibility genes involved in the recognition of bacterial peptides and elimination of intracellular bacteria. In addition, the intestinal microbiota is essential for the development of inflammation in colitis animal models.

There is no clear evidence for a single pathogenic microbe as the cause of the disease, but marked alterations emerge in microbial communities of IBD patients. Patients with IBD harbour fewer anti-inflammatory bacteria and/or more pro-inflammatory bacteria.

The 20th century has witnessed a steady increase in incidence of IBD and other auto-inflammatory diseases in Western industrialised countries. In less developed countries, with poor sanitation and crowded living conditions, these diseases have remained rare, but they are on the rise in those adopting a more Western lifestyle.

This raised the question whether it was possible that improved hygiene, and hereby clearing our bodies of parasitic worms and beneficial bacteria, affects our immune development and predisposes us to immunological diseases later in life. The current ‘hygiene hypothesis’ suggests that this increase is partly attributable to an immune dysregulation that includes both adaptive and innate immune systems.

Both cell-mediated and humoral mechanisms are involved in the adaptive immune system. The adaptive immune system is driven by activated T-helper cells [Th]. In humans, Th-1, Th-2, and Th-17 cells have been identified and are thought to be the main instigators of uncontrolled chronic inflammatory diseases. At least in Crohn’s disease, the adaptive immune system appears to be skewed towards the Th-1 and Th-17 pathways with the production of copious amounts of IFN-γ and IL-17.

In the hygiene hypothesis, it has been postulated that the strong Th2 response induced by the helminth parasites counterbalances the overactive Th1/Th17 response. As a consequence, in regions with a virtual eradication of parasitic infections in childhood, Th1/Th17 immune disorders would become more prevalent. However, new evidence has shown that besides an increase in Th1/Th17-mediated chronic inflammatory diseases [multiple sclerosis, IBD, and rheumatoid arthritis] there is also a concurrent increase of Th2-mediated allergic disorders, suggesting that not the Th1/17/Th2 balance but rather checks and balances between immunoregulatory and effector mechanisms are primary.

The effects of different helminths on animal models of IBD [D/TNBs colitis, IL-10 deficient colitis, and T-cell transfer colitis] have been extensively studied. Helminths seem to induce the production of IL-4, IL-5, and IL-13 by Th2 cells. This Th2 response suppresses the production of Th1 cytokines, reducing the severity of the colitis both in human IBD and mouse colitis studies. Second, helminths appear to induce regulatory T cells and activated macrophages. These cells diminish immune responses and autoimmunity, by producing IL-10 and TGF beta. Third, helminths seem to activate dendritic cells and macrophages and hereby avoid the activation of effector T cells, which induce inflammation and disease. Last, helminths alter the composition of the intestinal flora, resulting in an overall decrease of pro-inflammatory bacteria. Research in IL-10 gene-deficient mice with the parasitic helminth Heligmosomoides polygyrus has shown that these microbes favour the growth or suppression of certain bacteria. For example, members of the Lactobacillaceae family are significantly promoted.

Both the human hookworm [Necator americanus] and porcine whipworm [Trichuris suis] have been tested in clinical trials, although the majority of the trials have used the porcine whipworm. T. suis can colonise humans but doesn’t cause disease. It migrates to the terminal ileum and colon but does not invade the host and is therefore a potentially safe and good candidate for clinical use. People acquire whipworm infections by ingesting microscopic parasite ova [TSO]. The ‘therapeutic’ ova are obtained from pigs raised in pathogen-free environments.

The effect of T. suis colonisation was first studied by Summers et al. in 2003. Both patients with active Crohn’s disease and those with ulcerative colitis were included. Patients ingested one dose of 2500 ova. All patients improved clinically without any adverse events or laboratory abnormalities. A subsequent placebo-controlled study showed a significantly better improvement in the TSO treatment arm in patients with ulcerative colitis. An open-label study in patients...
with active Crohn’s disease showed a 79% clinical response to TSO with clinical remission in 72% of patients.11,12

To confirm this preliminary efficacy and to demonstrate superiority of TSO over placebo, Schölmerich et al. set up the first phase II prospective, randomised, double-blind, placebo-controlled, multicentre trial, comparing the efficacy and safety of fortnightly administration of 250, 2500 and 7500 TSO/15 ml suspension/day versus placebo for induction of remission in mild-to-moderately active uncomplicated Crohn’s disease [CD]. The primary efficacy endpoint was the proportion of patients achieving clinical remission (Crohn’s Disease Activity Index [CDAI] < 150 at end of treatment).

Interestingly, the results showed no significant superiority over placebo in any of the TSO treatment arms [% clinical remission at Week 12: 38.5 in TSO 250, 35.2 in TSO 2500, 47.2 in TSO 7500, and 42.9 in the placebo group], with p-values of, respectively, 0.6725, 0.8240, and 0.3006 between the different groups and placebo. The secondary efficacy variables did not show any advantage of TSO over placebo for the treatment of active CD either. Finally, none of the post hoc analyses could explain the high response rate in the placebo arm.

On the other hand, there was a clear dose-dependent immunological response (dose-dependent increase in blood eosinophil percentage and stool eosinophil-derived neurotoxin [EDN] levels and a dose-dependent specific humoral response to excretory/secretory [E/S] antigens of *T. suis* with seroconversion to IgG) after three administrations. This implies that the absence of superiority cannot be caused by a lack of viable *T. suis* eggs or hatched larvae because a clear pharmacodynamic response was observed.

The authors invoke several hypotheses to explain the absence of a therapeutic benefit. First, the duration of the treatment could be insufficient given the long-established disease [median 4–7 years] in this study cohort. If this were to be true, why would helminths fail to induce remission in the short term? To underscore this argument, Fleming *et al.*, have suggested that because of the protracted subclinical progression of auto-immune diseases and the various epigenetic contributors to the disease progression, a relatively longer treatment with helminths [6–12 months] may be desirable to achieve a clinical effect.11,12

The suggestion by the authors that prevention of disease relapse would have been a better primary outcome, falls into the same hypothesis. Also, it could well be that the ‘hygiene hypothesis’ is wrong or incomplete. The increase of auto-immune diseases in the past century simultaneously with the decrease in helminth infections may just be a marker for more general lifestyle changes. The fact that other trials of TSO, for other indications like allergic rhinitis, failed may just be a marker for more general lifestyle changes. The fact that other trials of TSO, for other indications like allergic rhinitis, failed to show superiority for the TSO arm, also contradicts the hypothesis.

Finally, the investigators suggest that the high placebo effect is triggered by the idea of swallowing a ‘live drug’. However objective biomarkers, which could counterbalance the subjective content of the CDAI, were also not affected by the TSO. The study would have benefited from a systematic endoscopic response assessment to help harness an exaggerated placebo effect or physician bias.

Virtually all current treatment options for IBD are directed toward the overactive immune response in IBD. It is clear that the enteric microbiota affects the production of cytokines and chemokines and hereby controls the T cell repertoire of the intestine. So manipulation of the gut microbiota to restore normobiosis has therapeutic potential in IBD and could be a good alternative to the current immunosuppressive therapies. The intestinal microbiota of patients can be influenced in different ways, first of all by changes in diet. Findings from different epidemiological studies revealed that a diet high in polyunsaturated fatty acid and meat and low in fruits, fibre and vegetables is the most common pattern associated with an increased risk in IBD. Low levels of Vitamin D also appear to be a risk factor for IBD. A number of clinical trials are being set up to further investigate the role of defined diets, either alone or in conjunction with the classical immunosuppressing agents.

A second option is to use probiotics. One probiotic cocktail, VSL#3, has shown beneficial effects for induction and maintenance of remission, mostly in UC patients and patients with pouchitis. However, most studies with probiotics in IBD have been negative, although some may have suffered from low sample size. In addition, heterogeneous preparations have been used as well as inconsistent outcome parameters and entry criteria. Most commercial preparations contain a relatively low number and diversity of bacterial species in comparison with the gut microbiota, and therefore may not be able to compete effectively against the complex established microbiota in the gut. Despite the negative findings, probiotics are widely used by patients.

Third, faecal microbial transplant [FMT], the transfer of the gastro-intestinal microbiota from a donor to a patient, has been explored as a treatment option in IBD. It is a highly effective therapy for recurrent and relapsing *C. difficile* infections [CDI]. The mechanism by which remission is obtained is believed to be colonisation by healthy donor microbiota, which suppresses toxin-expressing *C. difficile*. Since the dysbioses in CDI and IBD are similar, it is possible that FMT may also be effective as IBD treatment. The first controlled studies have generated conflicting results in UC and have been negative in patients with CD or pouchitis. Further studies into the optimal source of donor faeces, route of delivery, frequency of administration, and influence of concomitant diet are required before FMT is employed on a large scale.

In conclusion, although the data on dysbiosis and the impact of the microbiota on gut inflammation are expanding by the day, the study published in this issue of JCC adds to the growing number of failed attempts to conclusively demonstrate a beneficial therapeutic effect of the microbiota in human IBD. We need to return to the drawing board and find out a lot more about how the microbiota or other luminal contents dampen chronic inflammation.

**Conflict of Interest**

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**References**


