

Therapeutic use of Parasites in the Treatment of Inflammatory Bowel Disease

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Received: February 27, 2024; Accepted: March 11, 2024, Published: March 22, 2024

Introduction

- Helminths are multicellular invertebrates that colonize the gut of many vertebrate animals including humans
- This colonization can result in pathology, or it can lead to a commensal, even a symbiotic relationship
- Epidemiological data have linked helminth exposure to protection from immune disorders (allergies, autoimmune illnesses, IBD)
- Treatment of moderate to severe IBD involves the use of immune modulators, biologics and surgical intervention, which can cause life-threatening complications
- Their safety profile makes helminths or helminth products attractive as novel therapeutic approaches to treat IBD

Methods

- Meta analysis of available literature
- Helminths stimulate Th2 and immune regulatory pathways, which are targeted in IBD treatment
- Researchers investigate whether controlled parasitic infections can ameliorate the excessive immune responses underlying IBD

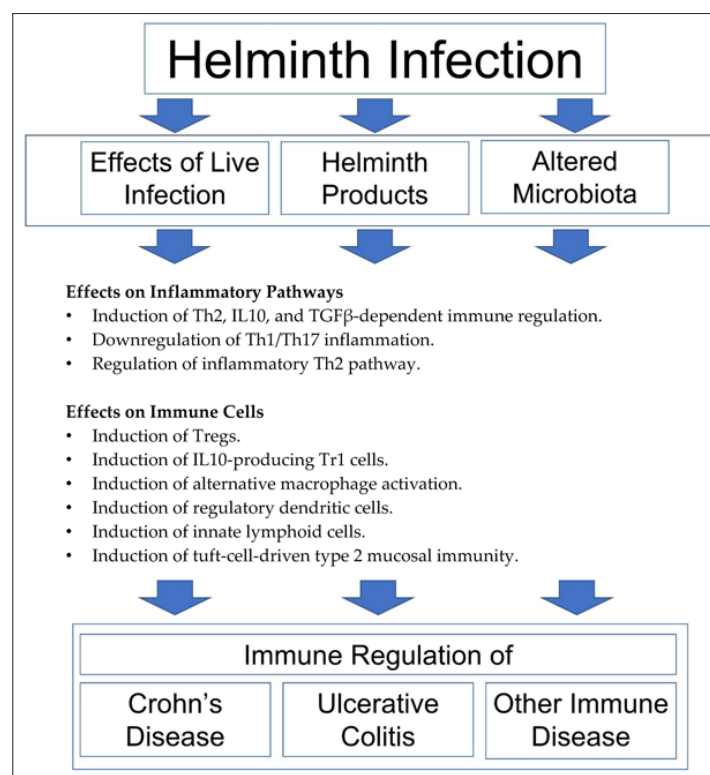


Figure 1: Mechanisms of Helminthic Immune regulation

Etiopathogenesis of IBD

- More than 200 genetic loci have been identified to be associated with the risk of IBD
- More than 10% of IBD patients have a family history
- CD has only 50% concordance between monozygotic twins and this number is even lower in UC
- This indicates that environmental factors and lifestyle exposures are also important in the pathogenesis of IBD (cigarette smoke, BMI, nutrient exposures, NSAIDs, intestinal infections)

Hygiene Hypothesis

- Helminth infections are most prevalent in geographies where sanitary conditions are poor and are often endemic in less industrialized parts of the world
- Accordingly, the rapid increase in the prevalence of immune disorders in the second half of the 20th century can be attributed to the dramatic decrease in the diversity of infectious exposures
- This decrease in diversity is associated with high-quality hygienic practices

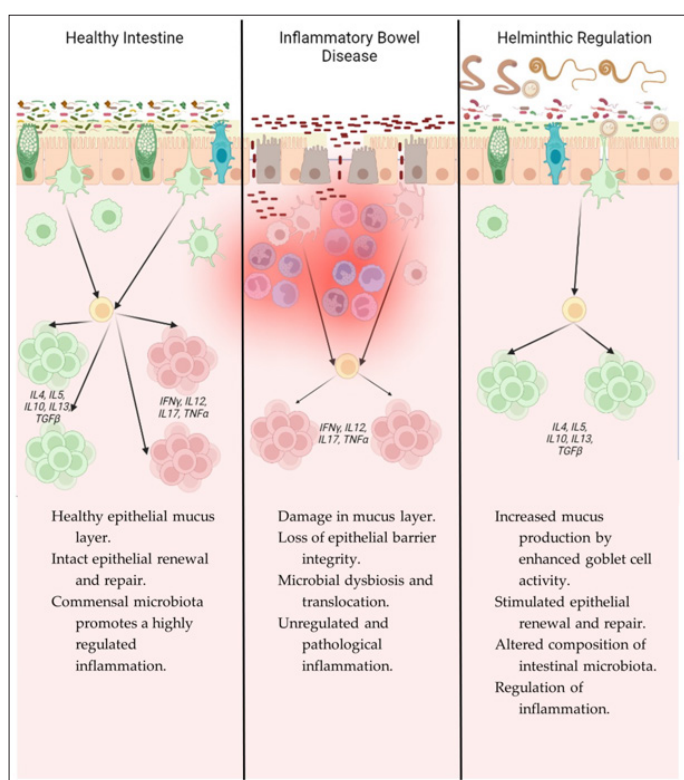


Figure 2: Immunological Comparison of Intestinal Mucosa in a Healthy State, Ibd, and After Helminth Infection

Results

- Phase 1 clinical trials for IBD have used two nematode species—*Trichuris suis* and *Necator americanus*
- The safety of TSO in IBD patients was first evaluated in an open trial in a small cohort of 7 patients with IBD, and again later in 12 patients in a randomized, double-blinded, placebo-controlled, dose escalation trial
- TSO was well tolerated in all doses, including the highest, and none of them caused any significant adverse effects
- Maintenance therapy with 2500 TSO every three weeks sustained clinical improvement without causing adverse effects

- A subsequent randomized, double-blinded, placebo-controlled trial treated 54 UC patients with 2500 TSO or placebo orally at 2-week intervals for 12 weeks - At 12 weeks 43.3% with ova treatment demonstrated improvement compared with 16.7% given placebo
- A similar trial for CD enrolled 29 patients, yielding a remission rate of 72.4% in patients treated with TSO for 24 weeks
- There was a larger trial in Europe, where 252 adults with CD received 6 total doses of 250, 2500, and 7500 TSO or placebo every 2 weeks, revealed an unexpectedly elevated clinical remission rate in the placebo recipients (42.9%) compared with the TSO recipients (38.5%, 35.2%, and 47.2%)
- Studies with Infective larvae (L3i) of *Necator Americanus* yielded noticeable side effects (pruritis, hookworm-related enteropathy) the side effects were less severe compared with the side effects of immune modulators or biologics
- P28 S-glutathione transferase (P28SGT), a protein derivative from a parasitic helminth, appeared safe when injected into CD patients in a multicenter, open-label, pilot Phase 2a study, and decreased disease activity index and inflammatory marker scores

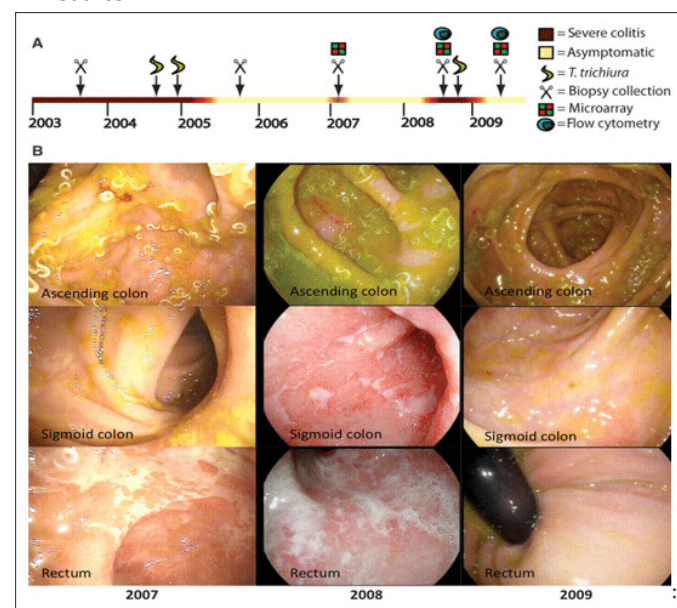


Figure 3: Examples of Gross Pathology Seen Upon Endoscopic Examination

Source: <https://www.science.org/doi/10.1126/scitranslmed.3001500>

Conclusion

- Research is still in its early stages
- Challenges remain in terms of standardizing treatment protocols, optimizing parasite dosages, and ensuring patient safety
- Striking a balance between potential benefits and risks is crucial
- Moreover, understanding the mechanisms by which parasitic infections modulate the immune system is essential for designing targeted and effective treatments

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