

Worms: A Remarkably Reasonable Treatment Option for Psoriasis

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ABSTRACT

There is a need to expand safe and effective treatment options for patients with moderate to severe psoriasis. This article hypothesizes one promising novel treatment option: *Trichuris Suis*. Epidemiological, experimental, and clinical evidence suggest that *Trichuris Suis* therapy may be both applicable and advantageous in the treatment of psoriasis. Epidemiologically, the de-worming of developed nations has been correlated with the increased prevalence of immune-mediated disease such as psoriasis. Additionally, the mechanisms of helminth immune regulation should mitigate the underlying immunopathology in psoriasis. Finally, safety and efficacy of *Trichuris Suis* has been demonstrated in other immune-mediated diseases such as Crohn's, ulcerative colitis, and multiple sclerosis with clinical responses in as many as 80% of patients. Evidently, there is ample evidence to warrant the investigation of *Trichuris Suis* therapy as a novel psoriasis treatment.

INTRODUCTION

Psoriasis is a chronic inflammatory immune-mediated disease of the skin and nails. Psoriasis is considered the most common immune-mediated disease, with an estimated global prevalence of 2-3% and an annual expenditure of \$3 billion in the United States alone.¹ The disease may dramatically impact quality of life and is associated with major cardiovascular and metabolic co-morbidities. The development of new therapies with favorable safety and efficacy profiles remains a priority in order to decrease disease burden and improve patient quality of life.

Helminths

There is evidence that helminths, eukaryotic parasitic worms, have been infecting humans since ancient times.^{2,3} As a result of their subsequent co-evolution, few people infected by helminths exhibit any symptoms of infection due to the parasites' ability to modulate the immune system of the human host.⁴ In fact, helminth infection often provides advantage to the human host. According to the "hygiene hypothesis" and its newest iteration, the "old friends hypothesis," modern sanitary advances with their concurrent de-worming of much of the developed world have been deemed responsible for the rise in immune dysfunction.^{5,6}

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Disclosures

The authors have no conflicts of interest to disclose.

Key words: Psoriasis, *Trichuris Suis* ova, helminth, old friend hypothesis, hygiene hypothesis, immune-mediated disease

Epidemiological studies have elucidated an inverse correlation between rates of helminth infections and prevalence of immune-mediated disease.⁷ In tropical environments where overcrowding, impure food sources, and helminth infection abound, the presence of autoimmune disease is rare. In the tropics, autoimmune disease prevalence is highest among those not infected by helminths. For example, although inflammatory bowel disease (IBD) prevalence is low in Arab Israelis with 60% helminth infection, IBD prevalence is high in Jewish Israelis with 10% helminth infection.^{8, 9} Consequently, distance from the equator, which corresponds with helminth infection rate, has been correlated specifically with psoriasis prevalence.¹⁰

Animal Modeling and Immune Regulatory Mechanism

The “old friend hypothesis” is theoretically plausible and gains support from epidemiological evidence. However, other environmental changes that coincided with improvements in sanitation also could be responsible for the observed increase in autoimmunity. The concept becomes most compelling when augmented with the results of experimental mouse modeling. Colitis, encephalitis, type 1 diabetes, and asthma mouse models have demonstrated helminthic-driven protection from disease.^{11, 12}

Helminth infection diverts the Th1 immune response to a strengthened Th2 response.^{7, 13-17} Th2 response is marked by secretion of interleukin (IL)-5, IL-9, IL-10, IL-13, immunoglobulin (Ig)E, and the recruitment of mast cells, eosinophils, and basophils.^{18, 19} Since Th1 and Th2 pathways display cross inhibition, Th1 and associated INF gamma, IL-12 and TNF-alpha cytokines are inevitably decreased. Helminthic therapy suppresses Th17 produced IL-17 and IL-23 cytokines, decreasing associated pro-inflammatory effects.^{20, 21}

Other immune regulations exhibited by helminth infection include the activation of regulatory T cells.²² These cells weaken the immune system by decreasing Th1 and Th2 responsiveness via their production of IL-10 and TGFβ molecules. Finally, helminth infection decreases the activation of effector T cells through modulation of regulatory dendritic cells and macrophages.

Helminths for the Treatment of Psoriasis

Based on the current disease paradigm for psoriasis, pathologic infiltration of T lymphocytes to the dermis and epidermis plays a crucial role in disease development. Historically, psoriasis has been characterized as a Th1 class pathology.²³ However, recent investigations have illuminated the additional involvement of Th17 T-cells.²⁴ Th17 produced IL-17 and IL-23 cytokines are fully expressed in psoriatic lesions and play an important role in the underlying mechanism of disease.^{24, 25} The ability of helminthic therapy to dampen excess Th1 and Th17 activity could make it an effective treatment for the underlying immunopathology. Furthermore, helminth activation of regulatory T cells and release of anti-inflammatory cytokines IL-10 and TGF beta described above may additionally mitigate psoriatic immune dysfunction. Finally, the ease of helminth administration via an oral route makes it an optimal alternative to current biologics.

Clinical Trials with *Trichuris Suis*

One helminth, the pig whipworm *Trichuris suis* ova (TSO), is thought to be particularly safe. With the ability to colonize the human colon without invading the blood stream or other organs, it has already begun to be orally administered to humans experimentally. To date, studies have been carried out in patients with IBD, allergic rhinitis, and multiple sclerosis. Preliminary studies have produced encouraging results.

Summers et al. performed the first clinical study of TSO in humans testing the therapy in three patients with ulcerative colitis (UC) and four patients with Crohn's disease (CD).²⁶ All patients showed clinical improvements after ingesting 2500 ova, and upon additional doses every three weeks, clinical improvement was maintained. Summer et al. performed a subsequent study with a larger sample size of 29 CD patients.²⁷ Enrolled patients were treated with 2500 TSO every three weeks for 12 weeks. By the end of the study period, 80% of patients experienced a clinically significant response to treatment. There were no patient reports of adverse events in either study.

In 2005, the first randomized controlled trial of TSO was performed in UC.²⁸ The study was double blind and placebo-controlled. Patients were treated with 2500 TSO every two weeks for 12 weeks. A

significantly greater proportion of patients in the TSO group (43.3%) improved than in the control group (16.7%), $P=.04$. A 12-week crossover in which patients were switched from their original study arms was integrated into the study, while blinding remained intact.²⁹ This crossover phase also revealed a significant improvement in TSO-treated patients (56.3%) compared to controls (13.3%), $P=.02$. No side effects were reported.

A recently completed study was designed to test safety in dose-escalation of a single TSO dose in CD patients.³⁰ It was a double-blind, placebo-controlled phase I study. Each of the three study doses was well-tolerated by patients, and there was no increase in likelihood of GI symptoms in experimental groups compared to control.

TSO also has been tested in other classes of immune-mediated diseases. In a double-blind placebo-controlled clinical trial in allergic rhinitis, 100 patients with grass pollen allergy were treated with either 2500 TSO or placebo every 3 weeks for 24 weeks.³¹ This study was the first that did not produce clinical improvements in patients. Instead, several days of diarrhea was seen as a side effect in one-third of patients. However, a recent study testing TSO as a therapeutic agent in relapsing and remitting multiple sclerosis (RRMS) added to the growing body of encouraging results.³² Five RRMS patients were treated with 2500 TSO every 2 weeks for 3 months. The number of MRI lesions, a measure of disease severity, decreased by a third on average by the end of the treatment period. Again, no side effects were reported.

Several studies investigating TSO treatment are ongoing in this burgeoning field. A large phase II study of TSO in CD is well under way in Europe, sponsored by Dr. Falk Pharma (TSU-2/CDA). A randomized phase I pilot study evaluating the safety and efficacy of TSO as a therapy for moderate to severe psoriasis is about to begin. TSO is being further examined in MS, rheumatoid arthritis, autism, and allergic rhinitis. Upon completion of these efforts, more valuable data will be available to help evaluate TSO efficacy in the treatment of these numerous immune-mediated diseases.

IMPACT AND FUTURE DIRECTIONS

Treatment of psoriasis with orally administered TSO may provide an additional novel treatment option for psoriasis, with the potential for an alternative side effect profile compared to currently available therapeutics. Its ease of administration may promote medication adherence and improved patient quality of life. Based on the growing theoretical, experimental, and clinical comprehension of helminth infection, intentional and controlled TSO exposure seems a promising treatment option for psoriatic disease. There is much enthusiasm to explore this hypothesis in clinical trials of TSO in psoriasis patients in the years to come.

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