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TSO: Trichuris Suis Ova; CNS: Central Nervous System; MS: Multiple Sclerosis; RRMS: Relapsing-Remitting Multiple Sclerosis

Mini Review

Therapeutic Administration of Trichuris Suis Ova as Alternative Treatment of Multiple Sclerosis: A Mini-Review

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Abstract

Autoimmune disorders like Multiple Sclerosis (MS), rheumatoid arthritis, and inflammatory bowel disease occur when your body's mounts a response to itself. Genetic predisposition is responsible for some of the response, while environmental factors contribute as well. Multiple sclerosis is a debilitating disease that impacts the brain, spinal cord, and optic nerves. There is an inverse correlation of exposure to helminths with prevalence of MS in helminth-endemic countries. This may be due to the alteration with the immunological response to antigens that accompanies the exposure to helminths. With the different molecules secreted by helminths that enhance tolerance in the human immune system to survive, interest in these secretory molecules for developing novel treatments against autoimmune diseases grew. There has been focus on *Trichuris Suis Ova* (TSO), eggs of a porcine helminth, as biologic for the treatment of autoimmune diseases. The results for TSO-based therapies as treatment for MS have been promising, in addition to these therapies being safe and well tolerated. However, there have been some contrasting reports with clinical outcomes. Therapeutic administration of *T. suis* ova or other products of this helminth as alternative treatment of multiple sclerosis should be further studied and thus provide enhancements in these immunotherapies.

Introduction

The prevalence of autoimmune diseases has increased during the last century, especially in the western world, and some of these diseases include Multiple Sclerosis (MS), Rheumatoid Arthritis (RA), and Inflammatory Bowel Disease (IBD). Multiple sclerosis is a neurological disorder characterized by sustained inflammation coupled with demyelination. These contribute to axonal loss and neurodegeneration which lead to Central Nervous System (CNS) atrophy [1]. In alignment with the "hygiene hypothesis", MS prevalence being concentrated in industrialized regions of the world may be linked to the possession of a "defective microbiome". Studies have shown that Toll-Like Receptor 2 (TLR2) signaling is a critical player in both the defective remyelination and the inflammatory component in MS [2]. In terms of the hygiene hypothesis and MS, the hygiene hypothesis includes that environmental Pathogen-Associated Molecular Patterns (PAMPs) are required to adequately regulate and "tune" innate immune responses, and individuals living in environments that are "too clean" have a "defective microbiome" that is defective in delivering TLR2-tolerizing PAMPs to the systemic immune system, resulting in poorly regulated immune systems and increased immune-mediated diseases [2]. This relationship between the gut microbiota and the hygiene hypothesis enhances the understanding of the pathophysiology of MS.

Different helminths used in animal and human models displayed a suppression of inflammatory activity with various autoimmune diseases, i.e. IBD, MS, lupus, RA, Graves' disease, and type 1 diabetes [3]. Considering the potential benefits and risks of applying a known infectious agent to patients inflicted with inflammatory conditions, *Trichuris suis* is a porcine whipworm that is like the human whipworm, *Trichuris trichiura*, was chosen as the promising treatment candidate [4]. Eggs of these trichurids are morphologically indistinguishable [5]. It has been shown that the ingestion of the ova of *T. suis* can lead to a self-limited colonization for a short period of time [6]. Unlike hookworms and ascarids, whipworms like *T. suis* possess a direct life cycle that is confined to the intestines. In humans, this porcine whipworm usually does not reach sexual maturity, and this makes colonizing the gut short-lived (weeks), which means that treatments need to be repeated at intervals in order to maintain hatched *T. suis* larvae in the non-natural human host [4].

Multiple Sclerosis

Multiple Sclerosis (MS) is a disabling, autoimmune disease of the brain and spinal cord and is characterized by selective destruction of myelin in the CNS neurons, which includes the optic nerve [7]. Relapsing-Remitting MS (RRMS) is its most common disease course and tends to affect women more than men [8]. As with other autoimmune diseases, the inverse association with MS prevalence with helminth exposure in helminth-endemic countries catapulted the notion of helminth-based therapy as a novel treatment option. Helminth therapy was first utilized in the treatment for MS in 2011 [9]. During this trial, five MS patients with newly diagnosed, treatment-naïve RRMS were administered orally with repeated doses of 2500 TSO over 12 weeks in which the baseline was compared to a treatment-controlled exploratory study. It was observed that this therapy was well tolerated amongst the patients, and that some favorable trends occurred in disease scoring. There was a decline from 6.6 at baseline to 2.0 at the end of TSO administration, in the mean number of new gadolinium-enhancing magnetic resonance imaging (MRI) lesions (n-Gd+) and two months post-TSO- treatment, the mean number of n-Gd+ rose to 5.8. There were some elevations in serum IL-4 and IL-10 levels in four of the five patients.

An open-label, MRI assessor-blinded trial included a run-in period for 8 weeks where patients were orally administered 2500 live TSO biweekly for 12 weeks [10]. An MRI was conducted with 3-week intervals. Neurological examinations and phlebotomy were performed at screening, baseline, and at weeks 6 and 12. Ten patients, two men and eight women, ages 24 to 55 years with relapsing MS were on the study. Criteria of the patients were a median disease duration of nine (4-34) years, a score of 2.5 (1-5.0) on the Expanded Disability Status Scale (EDSS), and three (2-5) relapses within the last two years. Six patients were subcutaneously treated with Interferon (IFN)-beta, and the four remaining patients received no other therapy. The TSO-treatment was well tolerated and with overall good compliance with no safety concerns. Two patients relapsed in the run-in period, and an individual patient suffered a single relapse and another patient two relapses during TSO-treatment.

During the run-in period, new MRI activity was seen in three patients in the run-in period (three 3-weekly scans) and in eight TSO-treated patients (four 3-weekly scans). Aside from eosinophilia, there were no changes shown in the treatment period [10].

In 2021, individual MS patients were given 2500 controlled TSO orally every 2 weeks for 12 months [4]. The Peripheral Blood Mononuclear Cells (PBMC) from five TSO treated MS patients and six placebo MS patients were assessed. *Trichuris suis* excretory/secretory antigen- specific IgG and IgE antibodies in serum continuously grew in numbers 12 months beyond treatment. An increased frequency of activated T cells, in particular HLA-DR+, was seen in TSO-treated patients with mass cytometry analysis. Similar kinetics within the antigen-specific T cell population, $CD4^+$ and $CD8^+$ T cells, were detected in both placebo and TSO-treated patients over time, while an increase of activated HLA-DR^+CD4^+ T cells in TSO-treated patients only. Occurrences of $Gata3^+$ Th2 cells and Th1/Th2 ratios were stable during TSO treatment; however, $Foxp3^+$ Treg frequencies was highly variable between individuals. A T. suis antigen-specific T cell expansion revealed greater variability with antigen-specific T cell recall responses and cytokine production between patients. These findings showed that the TSO-treated MS patients mounted a *T. suis*-specific T- and B-cell response but had a diverse range of cellular functionality and T cell responses with these individuals. This could provide an explanation for overall miscellaneous clinical efficacy involved [4].

Discussion

Efficacious yet safe ways to manage MS have been and continued to be studied. The utilization of TSO-based therapies to treat autoimmune diseases has been tested in a variety of clinical studies with some promising but also various disappointing clinical outcomes. The premise of helminth exposure causing protection against MS paved way to investigations with testing a helminth-based therapy. Human helminthic parasites were once thought of as a therapeutic choice. This was a cautionary option since a human carrier is needed as a source. Eggs from this source could potentially lead to pathogenic transmission [6]. It has been shown that human helminths in human subjects could be trialed at low doses without provoking symptoms [11]. Higher intensities may yield pathogenicity; therefore, safety considerations restrict the dose of the parasite. The human whipworm, *Trichuris trichiura*, only affects humans and non-human primates [12] It has a direct life cycle. As a non-natural human parasite, infection in humans with similar species such as *Trichuris muris* (from mice) or *Trichuris suis* (from pigs) can transpire, but the infection is brief and self-curing, and the parasites cannot finish their life cycle [12].

With MS, the main cause of pathology is a misdirected immune response against the myelin sheath. The Th1 and Th17 cells are believed to play a central role in MS in the Central Nervous System (CNS) [13]. The crosstalk between microglial and astrocytic cells in the CNS is important for the regulation of the neuroinflammation. A murine model of MS is Experimental Autoimmune Encephalomyelitis (EAE). Akin in nature to IBD, helminths aided as treatment for EAE in the murine model by slowing the progression of EAE through the suppression of Th1 and Th17 cells and initiating the production of Th2 cells, Tregs, and regulatory macrophages [14]. With limited cohorts in studies, patients receiving TSO-treatment, a high degree interindividual variability can take place. With the utilization of biologicals like TSO for therapies of immune-mediated diseases, such as with MS, future work should be on a larger scale in order to accommodate this interindividual variability of adaptive immune responses at the cellular level.

In order to achieve the best results, further development and optimization of helminth-based treatment for autoimmune diseases should occur. The treatments should be tailored in order to address the aforementioned variability and be inclusive of individual host cellular responses and to identify treatment "responder" and "non responder" patients, especially with complex diseases like MS [4]. Precision medicine is an innovative approach for disease definition at a higher resolution to accommodate a more precise focus of subgroups of disease with novel therapies, and with this strategy, biologicals like TSO, there may be more impactful for subgroups of MS patients in improving clinical treatment efficacy [15]. 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 [16]. 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 [16] and glycans have been shown to induce Th2 response [17].

Helminth therapy with living worms could cause pathology and could potentially be accompanied with controversy [18]. Also, the thought of infection with a living parasite may be a daunting task for some. With the immunomodulatory properties possessed by helminths, their excretory and secretory products have become a more attractive target for drug development [19]. Here, the use of immunomodulatory drugs derived from parasite material to allow testing in biological systems can serve as blueprints to provide a safer and more controllable therapeutic modality.

Conclusion

In Western countries, there is an association with improved sanitation and hygiene with higher autoimmune disease prevalence. This means there is an inverse correlation with helminth exposure and autoimmune diseases in certain places. Helminths have shown to secrete different products that can be tolerated in humans. This exploited them as use for therapeutic compounds to treat autoimmune diseases. Treatments with TSO seemed to be safe and well-tolerated when administered to patients with MS for treatment. Investigations on a larger scale with utilizing other excretory and secretory products in precision medicine are needed to further assess these biologics as alternative therapeutic options.

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