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REVIEW

An update on the use of helminths to treat Crohn's and other autoimmununе diseases

Aditya Reddy · Bernard Fried

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Abstract This review updates our previous one (Reddy and Fried, Parasitol Research 100: 921–927, 2007) on Crohn's disease and helminths. The review considers the most recent literature on *Trichuris suis* therapy and Crohn's and the significant literature on the use of *Necator americanus* larvae to treat Crohn's and other autoimmune disorders. The pros and cons of helminth therapy as related to autoimmune disorders are discussed in the review. We also discuss the relationship of the bacterium *Campylobacter jejuni* and *T. suis* in Crohn's disease. The significant literature on helminths other than *N. americanus* and *T. suis* as related to autoimmune diseases is also reviewed.

Introduction

This is an update from the previous review by Reddy and Fried (2007) on studies that use helminths to alleviate the symptoms associated with Crohn's Disease (CD). This review, unlike the previous one, considers the use of helminth therapy in several autoimmune diseases other than CD. We now place particular emphasis upon the use of helminth therapy with the hookworm *Necator americanus* which was not mentioned in Reddy and Fried (2007). Of the 43 references used in Reddy and Fried (2007), only three are cited herein. Therefore, this review cites references which for the most part did not appear in our previous review. McKay (2006) noted that there is much to be learned from a careful analysis of immuno-regulation in helminth-infected rodents and from an understanding of the immune status of acutely and chronically helminth-infected humans. Although two species of hookworms, *Ancylostoma duodenale* and *N. americanus*, commonly infect humans through contact with contaminated soil (Hotez et al. 2004), we have not seen papers on therapeutic interventions with *A. duodenale*. Therapy with *N. americanus* larvae is easier to use by physicians than the *Trichuris suis* ova (TSO) treatment because of the fewer number of treatments and more long lasting effects of the hookworm treatments. Though we will continue to use the term TSO in our review, the term should really be TSE, because the treatment is with *Trichuris* eggs not ova. The nematode egg consists of a shell, an ovum or embryo in various stages of development, and some residual yolk; therefore, this larval stage should be termed an egg rather than an ovum.

A. Reddy (✉) · B. Fried
Department of Biology, Lafayette College,
Easton, PA 18042, USA
e-mail: Adireddymd@gmail.com

Helminth therapy with *N. americanus*

Hookworm infection with both *N. americanus and A. duodenale* occurs predominantly among the worlds most impoverished people and is a common chronic infection, with an estimated 740 million cases, mainly in areas of rural poverty in the tropics and subtropics (de Silva et al. 2003). The major hookworm-related injury in humans occurs when the adult parasites cause an iron-deficiency anemia resulting from intestinal blood loss (Hotez and Pritchard 1995; Stoltzfus et al. 1997; Albonjco et al. 1998). The chronic anemia associated with moderate to severe hookworm infection is a handicap to the affected human and limits the individual's prospects of a better future (Joven et al. 2005). Despite its associated morbidity, hookworm infections have apparent beneficial effects on hosts suffering from diseases including CD which are linked to overactive immune systems. Some individuals, including

Dr. David Pritchard of the University of Nottingham, UK and Jasper Lawrence of Autoimmune Therapies, Tijuana, Mexico have infected themselves with hookworms and reported good results in regard to alleviating preexisting symptoms associated with a disease state (Svoboda 2006). Lawrence claims his severe asthma and seasonal allergies went into remission using the same helminthic therapy offered herein (Svoboda 2006).

CD, a type of inflammatory bowel disease (IBD), is a condition in which the lining of the gastrointestinal (GI) tract becomes inflamed, causing severe diarrhea and abdominal pain. The goal of treatments is to achieve long-term remission enabling CD patients to function normally in their everyday lives; our original review provides a more detailed definition of CD (Reddy and Fried 2007).

Mortimer et al. (2006) conducted a dose-ranging study to identify the number of hookworm larvae necessary to achieve a load of 50 eggs/g in human stool for therapeutic trials of asthma. In a double-blind study, ten healthy subjects without asthma or airway hyperresponsiveness to inhaled methacholine, received 10, 25, 50, or 100 *N. americanus* larvae to a patch of skin on the arm. The clinical use of methacholine is to mainly diagnose bronchial hyperresponsiveness caused by either hypersensitivity or hyperreactivity. In the Mortimer et al. (2006) study, subjects were examined weekly for 12 weeks and subsequently treated with anthelmintics. Though skin itching at the entry site and GI distress were common at the higher larval doses, respiratory function was normal. All doses in the range of 10–100 larvae resulted in at least 50 eggs/g in the stool in the eight subjects who completed the study. In summary, Mortimer et al. (2006) found that infection with 10 *N. americanus* larvae is well tolerated, and is a potentially suitable dose for use in preliminary clinical therapeutic trials.

Helminth therapy with *T. suis*

Summers et al. (2005a, b, c, 2006) have successfully utilized the pig whipworm, *T. suis*, in patients with IBD and further clinical trials are anticipated. *T. suis* is a porcine whipworm and though genetically similar to *T. trichiura*, does not propagate in the human intestinal tract (Bee 1976).

In the Summers et al. (2005a, b, c, 2006) studies, repeated inoculation of *T. suis* eggs was required and concern was raised by Van Kruiningen and West (2005) that aberrant migration of the developing larvae could occur. Van Kruiningen and West (2005) stated that *T. suis* larvae are invasive, and could migrate aimlessly in humans; they were concerned about the possibility of errant wanderings of *T. suis* larvae from the gut of the human to sites outside of the gut. In our opinion based on the biology and structure of *T. suis* larvae it is unlikely that these organisms could enter the human lymphatic or venous system by means of the gut submucosa. However, the remote possibility of errant larvae of *T. suis* establishing in vital organs or sites of humans may exist. Summers et al. (2006) stated that in their experience of providing more than 2,000 doses of TSO to more than 120 patients (some of whom received treatment for more than 4 years) adverse events associated with these treatments were rare. Initially, all subjects in the Summers et al. (2003, 2005a, b, c) and Elliott et al. (2007) studies had actively inflamed gut mucosa and many were on prednisone, azathioprine, 6-mercaptopurine or other immune suppressants during their course of treatment with TSO suggesting relative safety even in immune compromised hosts (Summers et al. 2006).

Hsu et al. (2005) were also concerned about the detrimental effects of TSO treatment in humans. However, Summers et al. (2006) countered these concerns by stating that hundreds of patients now have received this treatment in Europe without reported side-effects; if symptoms occurred, the causative agent could be easily treated with anthelmintics. To ensure patient safety, Belizario et al. (2003) suggested that subjects in a helminth study group could receive anthelmintics, such as albendazole or ivermectin, after completion of clinical trials.

Hymenolepis diminuta treatment against colitis in a rat model

Further reasons to proceed carefully with helminth therapy for colitis related disorders was presented by Hunter et al. (2007) who examined the ability of the tapeworm *H. diminuta* to affect the course of oxazolone-induced colitis (a TH2 model) in the rat. In the study, disease severity was assessed by gross and microscopic anatomy, myeloperoxidase and eosinophil peroxidase activity, and cytokine synthesis. Hunter et al. (2007) found that infection with *H. diminuta* caused a significant exacerbation of oxazolone-induced colitis. Interestingly, Hunter et al. (2007) have shown that *H. diminuta* infection is beneficial in other models of colitis. The information from their study is presented as a caveat to the position that parasitic helminths in general can be considered as a therapy for different inflammatory disorders without necessitating careful analysis of the immunologic basis of the condition.

Secondary bacterial infection associated with *Trichuris* therapy

Another confounding factor with nematode infections such as species of *Trichuris*, may be the potential for secondary bacterial disease in the gut. This issue was presented when Mansfield et al. (2003) described the natural infection of

swine with the porcine whipworm *T. suis* and the appearance of secondary infections with the bacterium *Campylobacter jejuni*. In their study, three-day-old germ-free pigs given dual infections with *T. suis* and *C. jejuni* had more frequent and severe diarrhea and significant pathological effects than pigs given either no pathogens, or only *T. suis*, or only *C. jejuni*. These pigs had significant hemorrhage and inflammatory cell infiltrates in the proximal colon where adult worms were found, and abscessed lymphoglandular complexes in the distal colon with intracellular *C. jejuni* also present. Mansfield et al. (2003) found that pigs given only *C. jejuni* had mild clinical signs and pathology whereas the combined effects of *T. suis* and *C. jejuni* produced significant site-specific disease and pathology.

Abner et al. (2002) developed a swine model in which natural host resistance to *C. jejuni* was altered by experimental infection with *T. suis*. Pigs naturally colonized with *C. jejuni* experienced colitis because of the invasion of the bacterium approximately 21 days after exposure to *T. suis*. Abner et al. (2002) found that in addition to mechanical damage from worms, soluble products released by *T. suis* contributed to intestinal epithelial cell (IEC) damage at the site of worm attachment. Because campylobacteriosis, associated with *C. jejuni* infection, is characterized by tissue injury in the gut, it may be interesting to study this kind of interaction in humans as a potentiator of patient morbidity.

Other autoimmune diseases

Based on the hypothesis that chronic inflammatory bowel disease might be inhibited by stimulating a Th2 immune environment, Summers et al. (2005a, b) modified disease pathology in 29 CD and 54 ulcerative colitis (UC) patients by inoculating them with TSO. Previous studies involving animals have shown that parasite infection can alter the course of autoimmune diseases (Reddy and Fried 2008). Understanding mechanisms by which helminths manipulate immune responses and modulate autoimmune diseases such as IBD, rheumatoid arthritis and Type 1 diabetes may help to develop novel therapies for these diseases.

Autoimmune liver disease was modulated by active helminth infections in a study involving 4,117 patients who were admitted to hospitals in Okinawa, Japan, between 1988 and 2006 (Aoyama et al. 2007). This study is worth mentioning since CD also is of autoimmune etiology, and future studies of CD with *Strongyloides stercoralis* therapy may be warranted. The case-control study of Aoyama et al. (2007) described the prevalence of infection among patients with autoimmune liver diseases, such as primary biliary cirrhosis, autoimmune hepatitis, and primary sclerosing cholangitis. Aoyama et al. (2007) hypothesized that immunomodulation by *S. stercoralis* infection may lower the incidence of autoimmune liver disease.

The loss of helminth parasites in humans has been considered a public health success, but it is possible that eradication of these organisms has unforeseen consequences (Elliott et al. 2007; Fleming and Fabry 2007); epidemiological studies suggest that helminths may protect against some atopic and immune-mediated diseases (Reddy and Fried 2008). For example, Holgate and Lack (2005) noted that about one-half the population of developed countries currently suffer from atopy, asthma, or another allergic conditions; they also noted that the prevalence of allergic disease in the general population has increased alarmingly over the past 25 years, particularly in Western industrialized countries. Citing autoimmune conditions, Jacobson et al. (1997) estimated that 3% to 5% of the USA population suffers from immune-mediated diseases such as insulin-dependent diabetes, IBD, connective tissue disease, or multiple sclerosis (MS). The Correale and Farez (2007) double-cohort study of 12 patients suggested that parasitism in MS is associated with substantial clinical, magnetic resonance imaging (MRI) and immunological benefits; these findings are consistent with the hygiene hypothesis which has gained increased clinical support and is of academic interest. During a 54-month follow-up period, parasite-infected MS patients in the Correale and Farez (2007) study showed a significantly lower number of exacerbations, minimal variation in disability scores (a method of quantifying disability in MS), as well as fewer MRI changes when compared with uninfected MS patients.

The observation that allergies and autoimmune responses are increasing at a similar rate in industrialized nations, appears to undermine the hygiene hypothesis. Allergy researchers in the 1990s initially believed that reduced exposure to microorganisms failed to prime the Th1 response, which then led to overcompensating Th2 activity and resulted in allergies. The observation that allergies and autoimmune responses are increasing at a similar rate in industrialized nations, appears to undermine the hygiene hypothesis. The old friends hypothesis, as postulated by Graham Rook, modifies the hygiene hypothesis by proposing T regulator cells can become fully effective only if they are stimulated by exposure to microorganisms and parasites that have low levels of pathogenicity, and which have coexisted with human beings throughout our evolutionary history (Hadley 2004). Graham Rook, a professor at the Center for Infectious Diseases and International Health at the Royal Free and University College Medical School in London, UK, notes that many autoimmune diseases including CD have deficits in regulatory T cell activity (Hadley 2004). Rook et al. (2004) stated that a further role of the "old friends" and of the regulatory T cells that they induce might be to maintain the levels of regulatory IL-10 secreting macro-

phages and antigen-presenting cells, which are depleted in asthma and CD.

McKay (2006) stated that the ultimate reward from helminth therapeutic studies will most likely be a more comprehensive knowledge of immunity, novel ways to intervene in the immune response to alleviate autoimmune and allergic diseases (growing concerns in economically developed areas), and the eventual development of helminth therapy for patients suffering from specific inflammatory, autoimmune or allergic disorders. With continued research in the field of helminth therapies, it may be possible that after remission is achieved, endoparasites will one day offer an alternative or adjunct to immune suppressive therapy (Croese and Spear 2006; Croese et al. 2006a, b).

A link between atherosclerosis and helminth infections

Schoenfeld et al. (2001) summarized the diverse aspects of the interrelationship between the immune system and atherosclerosis. In the last decade, it has been realized that atherosclerosis, an inflammatory process, may have infectious and autoimmune components (Schoenfeld et al. 2001). In addition to the treatment of autoimmune disorders the anti-inflammatory effects of helminth infection are prompting interest and research into inflammatory diseases. The pathology of heart disease and arteriosclerosis has similar epidemiological profiles as autoimmune diseases—both conditions involve inflammation. Recent research has focused on the eradication of helminths to explain this discrepancy (Magen et al. 2005). Magen et al. (2005) stated that if the hypothesis that helminthic infections impact atherosclerosis is correct, it should be taken into consideration in atherosclerosis immunomodulation therapy and particularly in the design of vaccines and vaccine trials.

Concluding remarks

In the developed world, there has been a steady and simultaneous increase in at least three groups of disease: (1) allergies, (2) IBDs; e.g., CD and UC and (3) autoimmunity (e.g., type 1 diabetes and MS) all of which contain aspects of immunodysregulation (Rook et al. 2004). It is hoped that the development of helminth therapy may alleviate suffering from these specific inflammatory, autoimmune, or allergic disorders (McKay 2006).

Several large studies are under way as mentioned in such a popular venue as the NY Times. A recent article mentions that TSO is being tried on patients with MS, CD, and hay fever in the United States, Australia, and Denmark, respectively (Velasquez-Manoff 2008). The article mentions that in Germany, scientists are planning studies using TSO on humans with on asthma and food allergies and other labs are investigating similar treatments with *N. americanus*. Radford-Smith (2005) established that treatment of CD patients with *T. suis* is safe and effective in the short term, even with concurrent immunosuppressive therapy. In summary, both TSO and hookworm larval treatments appear to be well tolerated, and safe at therapeutic doses.

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