Helminth Regulation of Immunity: A Three-pronged Approach to Treat Colitis

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Abstract: By reputation, the parasite is a pariah, an unwelcome guest. Infection with helminth parasites evokes stereotypic immune responses in humans and mice that are dominated by Th-2 responses; thus, a hypothesis arises that infection with helminths would limit immunopathology in concomitant inflammatory disease. Although infection with some species of helminths can cause devastating disease and affect the course of microbial infections, analyses of rodent models of inflammatory disease reveal that infection with helminth parasites, or treatment with helminth extracts, can limit the severity of autoimmune inflammatory disease, including colitis. Intriguing, but fewer, studies show that adoptive transfer of myeloid immune cells treated with helminth products/extracts in vitro can suppress inflammation. Herein, 3 facets of helminth therapy are reviewed and critiqued: treatment with viable ova or larvae, treatment with crude extracts of the worm or purified molecules, and cellular immunotherapy. The beneficial effect of helminth therapy often converges on the mobilization of IL-10 and regulatory/alternatively activated macrophages, while there are reports on transforming growth factor (TGF)-β, regulatory T cells and dendritic cells, and recent data suggest that helminth-evoked changes in the microbiota should be considered when de...
IL-10, interferon (IFN)-γ or signal transducer and activator of transcription (STAT)-3, is implicated in T cell function, underscoring the previously suspected importance of T cells in the development of IBD.14-16

Early efforts in the characterization of ulcerative colitis and Crohn’s disease suggested that these closely related diseases differed in terms of the T-cell subsets driving the disease. Specifically, Crohn’s disease was felt to be driven by T helper (Th)-type1 cells (characterized by the expression of the transcription factor Tbet) and the corresponding cytokines IFN-γ IL-6 and IL-12, whereas ulcerative colitis was driven by Th2 cells (characterized by the transcription factor GATA3), which secrete IL-4, IL-5, and IL-13.17,18 The original Th1–Th2 paradigm has evolved to include many other T-cell subsets. Important to IBD are T regulatory cells (Tregs), characterized by the expression of the transcription factor FOXP3 and the secretion of IL-10 and Th-17 cells, characterized by the expression of the transcription factor RORγt and production of IL-17 and in some instances, IFN-γ and IL-22.19,20 Th17 cells and Tregs are implicated in both Crohn’s disease and ulcerative colitis; Th17 cells are thought to play a pathogenic role, whereas Tregs play a crucial anti-inflammatory and immunoregulatory role. Transforming growth factor (TGF)-β is important in influencing the development of Th17 and Tregs and molecules, such as mothers against decapentaplegic homolog (SMAD)-3, SMAD7, and SMAD ubiquitin regulatory factor, that control TGF-β signaling, feature among genes implicated by genome wide association studies (GWAS) in the pathogenesis of IBD.14-16 Likewise, defects in IL-10 receptor (IL-10R) signaling can drive the development of severe forms of very early onset IBD, whereas IL-23R loss-of-function mutations have been shown to be protective in ulcerative colitis and Crohn’s disease.14-16

Mononuclear phagocytes, dendritic cells (DCs) and macrophages, have emerged as central to the pathogenesis of IBD. Macrophages are the most abundant leukocytes in the healthy intestinal lamina propria and serve important functions such as phagocytosis and degradation of microorganisms and dead cells, as well as production of mediators that drive epithelial cell renewal.21 They also produce IL-10 that not only promotes the survival and function of FOXP3+ Tregs but also serves to dampen responses to microbial pathogen-associated molecular patterns.22,23 In a dramatic illustration of the importance of the latter, mice lacking the IL-10R on macrophages develop spontaneous colitis in a manner reminiscent of very early onset IBD, harboring loss-of-function polymorphisms within the IL-10R1 gene.24

Critical to the differentiation and function of intestinal T cells are DCs, professional antigen-presenting cells present at all mucosal surfaces where they continuously sample their environment and use their vast array of pattern-recognition receptors. These cells migrate from mucosal sites to mesenteric lymph nodes where they provide T-cell stimulation by means of major histocompatibility (MHC)-peptide complexes in the context of costimulatory molecules. Importantly, they influence Th-cell polarization by means of various soluble and membrane-bound molecules, including IL-1β, IL-6, IL-10, IL-12, IL-18, TGF-β, OX40 ligand, IFN-γ, and retinoic acid. The interplay of immunostimulatory and suppressive activities of DCs plays a central role in the induction of immune responses and the maintenance of intestinal immune homeostasis. In the steady state, intestinal DCs are likely tolerogenic. However, in the context of intestinal inflammation, they can drive proinflammatory responses such as promoting Th1 and Th17 cell development.24,25 DCs from inflamed tissue of IBD patients’ show enhanced Toll-like receptor (TLR) expression, maturation, and expression of activation markers. In Crohn’s disease, this is associated with increased IL-6 and IL-12 expressions.25 In ulcerative colitis, colonic DCs seem to drive T helper cells toward a Th2 phenotype.26

Innate lymphoid cells (ILCs) are recently described cells that produce cytokines traditionally associated with T cells. Analogous to the Th1–Th2 paradigm, ILCs are grouped into 3 distinct subsets based on the expression of transcription factors and cytokines27: ILC1 expresses Tbet and secretes IFN-γ; ILC2 expresses GATA3 and secretes IL-5 and IL-13; and ILC3 is analogous to Th17, expresses RORγt and secretes IL-17 and IL-22. ILC1 may be expanded in the ileum of patients with Crohn’s disease28, whereas IL-22 producing ILC3 may be protective.29 Less data link ILC2 to the pathogenesis of IBD. Interestingly, it is becoming evident that ILCs and T cells regulate one another and so, it may be difficult to assess 1 cell type without considering the other. Many of the T cell–expressed cytokines associated with IBD are produced by ILCs; thus, despite the low numbers of intestinal ILCs, their role in the pathogenesis of IBD may be greatly underappreciated.

Using Viable Infections to Treat IBD

The host–parasite relationship is one of coevolution: endoparasites seek food and shelter from their hosts, and this comes at a cost to the host. Consequently, the host evokes mechanisms to recognize and destroy/eliminate the parasite, whereas the parasite works to undermine such attempts by hiding from or manipulating the immune system through the release of molecules that directly suppress immune cell activity or promote the production of host immunoregulatory/immunosuppressive mediators30 (Fig. 1).

By definition, a parasite harms its host, harm that ranges from minor loss of nutrients to fatality; yet at the same time
parasites that conferred a selective advantage on its host, say through reduced susceptibility to other diseases, would reap the benefit of having continued access to food and shelter. The evolutionary forces driving this relationship can be complex. Given that helminth infections of mammals are often chronic, one would intuitively accept that a successful parasite would not only evade the host’s attempts to eradicate it, it would also impart a parallel health benefit to the host. Although seemingly paradoxical, the concept of a “harmonious parasite” is not new.30,31

The eradication of parasitic helminths from westernized societies32 correlates with increases in the incidence and prevalence of autoinflammatory diseases, including IBD.33 However, the same observation applies to reductions in microbial infections or increases in a high-fat diet in developing regions of the world and the emergence of IBD. Although intriguing, epidemiological data do not allow statements of causality, but do generate testable hypotheses, which in the context of infection with helminth parasites, have been described as “the hygiene hypothesis, old friends hypothesis or microbial deprivation hypothesis.”6,32,34,35 Thus, the following questions can be posed: (1) does infection with a helminth parasite limit the extent or severity of concomitant disease in the host? and (2) if so, can this be applied to the treatment of other diseases, in this instance IBD?

The first full report on a parasitic helminth being given to potentially ameliorative colitis showed that infection with the rat tapeworm Hymenolepis diminuta, in a prophylactic regimen, alleviated some of the intestinal dysfunction but had minimal effect on the colonic histopathology that characterizes dextran sodium sulfate (DSS)-induced colitis.9 Since then, analyses of a variety of models of colitis have repeatedly shown that mice infected with helminth parasites have significantly less severe disease (Table 1). Suppression of colitis has been observed with helminths (1) where the mouse is a permissive host (Trichuris muris and Heligmosoides polygyrus bakeri) or (2) a nonpermissive host (Trichinella spirali and H. diminuta), (3) where the parasite does significant (T. spiralis and Nippostrongylus brasiliensis), some (T. muris and H. polygyrus), or no tissue damage (H. diminuta) to the host, and (4) where the parasite does not seek to establish in the colon (T. muris, H. polygyrus, T. spiralis, H. diminuta, Schistosoma mansoni and Taenia crassiceps) (Table 1). This suggests that the anticolitic effects of these parasites are systemic, and this is borne out of the fact that infection with this same range of helminths can suppress inflammation beyond the gut, such as arthritis and diabetes.48 In addition, the ability of a range of parasites to inhibit colitis in a variety of models suggests common anti-inflammatory mechanisms.

**TABLE 1. Mice Infected with Helminth Parasites Have Significantly Less Severe Colitis**

<table>
<thead>
<tr>
<th>Species</th>
<th>Effect of Infection</th>
<th>Proposed Mechanism</th>
<th>Ref.</th>
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</thead>
<tbody>
<tr>
<td>Nematodes</td>
<td></td>
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<tr>
<td><em>Heligmosoides polygyrus</em></td>
<td>Inhibited DSS-colitis</td>
<td>Regulated IL-1β, TNF-α, IL-6, and MPO concentration, macrophage infiltration, and changed opioid expression</td>
<td>36</td>
</tr>
<tr>
<td><em>Heligmosoides polygyrus</em></td>
<td>Inhibited colitis in IL-10&lt;−/−&gt; mice</td>
<td>Blocked mucosal Th1 cytokine production</td>
<td>37</td>
</tr>
<tr>
<td><em>Heligmosoides polygyrus</em></td>
<td>Improved colitis in IL-10&lt;−/−&gt; mice</td>
<td>Suppressed LPMC IL-17 production</td>
<td>38</td>
</tr>
<tr>
<td><em>Heligmosoides polygyrus</em></td>
<td>Protected RAG mice IL-10&lt;−/−&gt; T cells-reconstituted from colitis</td>
<td>Reduced the capacity of the intestinal mucosa to make IFN-γ and IL-17</td>
<td>39</td>
</tr>
<tr>
<td><em>Heligmosoides polygyrus</em></td>
<td>Inhibited TNBS-colitis</td>
<td>Blocked IFN-γ and IL-12 p40 release and promoted IL-4, IL-5, IL-13, and IL-10 secretion</td>
<td>40</td>
</tr>
<tr>
<td><em>Trichinella papuae</em></td>
<td>Decreased the severity of DSS-colitis</td>
<td>Increased IL-10 mRNA in colon tissue</td>
<td>41</td>
</tr>
<tr>
<td><em>Trichinella spiralis</em></td>
<td>Inhibited DSS-colitis</td>
<td>Enhanced regulatory cytokine and Treg cell recruitment</td>
<td>42</td>
</tr>
<tr>
<td>Trematodes</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><em>Schistosoma mansoni</em></td>
<td>Attenuated TNBS-colitis</td>
<td>Diminished IFN-γ and enhanced IL-4 production</td>
<td>43</td>
</tr>
<tr>
<td><em>Schistosoma mansoni</em></td>
<td>Attenuated DSS-colitis</td>
<td>Induced Th2 cytokines</td>
<td>44</td>
</tr>
<tr>
<td>Cestodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Hymenolepis diminuta</em></td>
<td>Reduced DNBS-colitis</td>
<td>Increased intestinal Foxp3 mRNA and markers of AAMs</td>
<td>45</td>
</tr>
<tr>
<td><em>Hymenolepis diminuta</em></td>
<td>Reduced DSS-colitis</td>
<td>Increased colonic IL-10 mRNA and splenocytes-produced IL-10</td>
<td>46</td>
</tr>
<tr>
<td><em>Taenia crassiceps</em></td>
<td>Decreased DSS-colitis</td>
<td>Decreased systemic levels of proinflammatory cytokines and increased levels of IL-4 and IL-10</td>
<td>47</td>
</tr>
</tbody>
</table>

FoxP3, forkhead box P3; IL, interleukin; LPMC, lamina propria mononuclear cells; MPO, myeloperoxidase; TNF, tumor necrosis factor.
Indeed, and not surprisingly, the literature on suppression of colitis by infection with helminth parasites tends to converge on a small number of regulatory factors, typically the induction of IL-10, TGFβ, and IL-25 (both would inhibit inflammatory mediator production), regulatory T cells, subtypes of regulatory macrophages, with lesser information on regulatory B cells.

The power of using helminth parasites is that the inhibition of the colitis is a consequence of the natural immune response to the helminth. The goal is not targeting a single molecule or pathway, rather the suppression of colitis is the outcome of the complex and multifaceted immune response needed to recognize and eradicate the worm and reset the immune homeostatic set-point, and any direct contribution helminth-derived molecules play in suppressing immune cells. For instance, systemic delivery of recombinant IL-10 has not fulfilled its promise as a treatment of IBD, yet many of the anticolitic effects associated with helminth infection were reduced by concomitant in vivo neutralization of IL-10. In a similar fashion, Lactococcus engineered to express IL-10 effectively blocked colitis in animal models, and may be safe for use for IBD. Presumably, the benefit of IL-10 as a component of the anticolitic effect after infection with helminths is due to sustained release into the correct microenvironment. Similarly, promoting TGFβ activity can be of therapeutic value in IBD, and although this raises the specter of fibrotic disease, one might argue that TGFβ mobilized in response to infection with helminths could exploit the anti-inflammatory effects and not the profibrotic activity of this cytokine. Finally, mobilization of immune regulatory cells as a response to helminth parasites could direct the development of cellular immunotherapies (see below).

The analysis of rodent-helminth systems also reveals potential new therapeutic approaches to colitis. In humans and mice, the immune response to infection with helminth parasites is typically Th2-dominated, where early production of IL-25 is required. It has recently been shown that blocking IL-25 reduces the suppression of dinitrobenzene sulfonic acid (DNBS)-induced colitis in mice infected with H. diminuta. Reciprocally, IL-22−/− mice (IL-22 promotes antibacterial responses and can antagonize IL-25) infected with H. diminuta had negligible DNBS-induced colitis, prompting the suggestion that anti-IL-22 antibodies could be used to enhance the anticolitic effect of infection with helminths.

The gut epithelium is emerging as a determinant of the host response to helminths that seek to reside in the intestine. Tuft cells in the epithelial layer have been identified as taste-chemosensory cells and a major source of IL-25 that likely affects innate lymphoid cells (ILCs)-type 2 to promote Th2 immunity and the generation of IL-4 that promotes Tuft cell differentiation as a positive feedback loop to enhance Th2 immunity and counter the helminth. These studies contribute to 2 areas under analysis in the context of IBD, the role of IL-25 and the role of ILC5, each has been shown to be anti-inflammatory in specific model systems and as such could be targets of future therapeutics for IBD. H. diminuta cultured on epithelial cells lines evokes IL-25 production that aligns exactly with the permissive-ness of the host species. Thus, epithelial cells derived from the nonpermissive mouse produce IL-25 in response to the worm, whereas those from the permissive rat host have a negligible IL-25 response: mice, but not rats are protected from DNBS-induced colitis by infection with H. diminuta.

Other alarmins (e.g., IL-33 and TSLP [thymic stromal lymphopoietin]) produced after helminth infections, have been implicated in subsequent anticolitic effects. For example, TSLP−/− mice infected with T. muris have reduced synthesis of Th2 cytokines, overproduction of the Th1 cytokines IL-12/23p40 and IFN-γ, and have worse DSS-induced colitis compared with wild-type mice. In vitro analysis with murine bone marrow–derived macrophages revealed that an alternatively activated phenotype as defined by canonical marker molecules was increased by cotreatment with IL-33; a variety of regulatory macrophages have been found to suppress colitis in murine model systems.

The intestinal microbiota, as a consequence of dysbiosis, altered metabolism, or activity of an opportunistic pathobiont, is a critical element in the pathophysiology of IBD. Could the inhibition of colitis by infection with helminth parasites be mediated, at least in part, by means of the microbiota? This could occur as a direct interaction between worm and bacteria (e.g., bacteria are required for the hatching of T. muris eggs) or in response to the immune reaction against the worm, such as changes in goblet cell number or mucus consistency that would be expected to affect the microbiota.

Infection with intestinal helminth parasites affects the composition of the gut microbiota, and this impacts host immunity: infection with H. polygyrus reduced Helicobacter-induced gastric atrophy, impaired antiviral immunity independent of the microbiota, and increased the Lactobacillaceae family of bacteria. Four of 5 Rhesus monkeys infected with the helminth Trichuris trichiura showed improvement in idiopathic chronic diarrhea, and this was accompanied by the expansion of the bacterial phylum Tenericutes. It was recently shown that the ability of H. polygyrus to suppress airway inflammation was dependent on the microbiota and operated through short-chain fatty acid signaling through the G protein–coupled receptor-41. Moreover, Nod2−/− mice infected with T. muris or H. polygyrus had increases in goblet cell numbers and less small bowel histopathology that was driven by a loss of Bacteroides vulgatus and increased numbers of Clostridia spp. The same study showed that Orang Ashi Malaysians infected with intestinal helminths have reduced bacteroides and increased clostridiales, and this pattern was reversed after anthelmintic treatment. Collectively, these studies highlight the impact of helminths on the host intestinal microbiota and the potential of the latter to contribute to an anticolitic effect associated with a therapeutic helminth. The translation of these animal studies to human IBD awaits verification and is ultimately dependent on demonstration of the effectiveness of infection with viable helminths to reduce or block IBD, at least in defined patient cohorts.

Animal studies overwhelmingly support the concept of a therapeutic helminth to treat IBD, but what of side effects? Few studies address this issue. The possibility of iatrogenic disease...
must be acknowledged, and it has been shown that infection with helmints can worsen the outcome of infection with *Myobacterium tuberculosis*. Infection with *H. polygyrus*, *Trichuris muris*, and *H. diminuta* exaggerated the severity of *Citrobacter rodentium*-induced, spontaneous colitis in multidrug receptor (Mdr) 1a knockout, and oxazolone-induced colitis in mice, respectively. Given the impact on helmints on the microbiota, one might speculate on the potential of a bacterial pathobiont to emerge in an individual as a consequence of a therapeutic helmint. Data on helmints in IBD are discussed below and to date, there are no reports on significant side effects in patients treated with *Trichuris suis*, the pig whipworm that will neither establish nor reproduce in humans and should be restricted to the gut (1 of the 5 Rhesus monkeys infected with *T. trichiura* died, and it is unclear if this was due to the severity of the idiopathic chronic diarrhea or in any way precipitated by the infection.

**Is Infection with Helminth Parasites of Benefit in IBD?**

A 6-patient study presented in abstract form at Digestive Disease Week in 1999 heralded the way for small trials in Crohn’s disease and in ulcerative colitis by Weinstock et al using *T. suis*; both revealed statistically significant improvements in disease in patients who received the helmint. These tantalizing data have been complemented by case reports of patients self-administering infective helmints to relieve their disease and the intriguing possibility that low infectivity with the human hookworm, *Necator americanus*, and gluten microchallenge can be used to treat celiac disease.

Randomized clinical trials (RCTs) on the helminths effect in IBD are few (Table 2). As such, the evidence for this intervention remains inconclusive. A recent Cochrane meta-analysis found 2 RCTs with a total of 90 participants; the authors concluded that there is insufficient evidence for the safety or effectiveness of helmintic therapy in IBD.

The first study included 7 patients with refractory IBD (4 Crohn’s disease and 3 ulcerative colitis) who were given a single dose of 2500 live *T. suis* ova (TSO): 6 patients achieved remission for 8.3 weeks, one patient with Crohn’s disease did not achieve remission but reportedly had clinical response, and no adverse events were reported. Four patients were given prolonged therapy (2500 TSO every 3 weeks for ~28 weeks): 3 (2 with ulcerative colitis and one with Crohn’s disease) entered remission and continued for more than 1 year of follow-up, whereas the remaining patient with Crohn’s disease had a significant drop in their Crohn’s Disease Activity Index (CDAI) from 526 to 213.

Subsequently, Summers et al reported the results of 2 studies with TSO in IBD. The Crohn’s disease study was an open-label study, enrolling 29 patients with moderately active disease, who received 2500 TSO suspension every 3 weeks for 24 weeks. This resulted in remission in 19 of 29 patients (65.5%) and a clinical response in 22 of 29 (75.9%) within 12 weeks (remission defined as CDAI <150 and response as CDAI drop >100 points). No side effects were documented. The ulcerative colitis study was a double-blind RCT where 54 patients were assigned to 2500 TSO (n = 24) or placebo (n = 30). There was a significant difference between TSO intervention and placebo in terms of clinical response: 43.3% versus 16.7% (P = 0.04). However, there was no difference in remission between the 2 arms of the study. No side effects were documented.

Sandborn et al randomized 36 patients with mild-to-moderate Crohn’s disease with a single dose of placebo (n = 9) or TSO (500, 2500, 7500; n = 9 each group). The study found that TSO was safe and tolerable at the highest dose of 7500 without side effects. Some patients did experience diarrhea with 2500 or 7500 TSO.

More recently, TRUST-I (phase II, multicenter, RCTs) were conducted in the USA and Europe, respectively, with Crohn’s disease. TRUST-I, enrolling 250 patients with moderate-to-severe disease (giving half a placebo and half 7500 TSO), did not meet the primary endpoint of favoring response or the secondary endpoint of achieving remission. The TRUST-II trial randomized 252 patients with mild-to-moderate disease to placebo or TSO (250, 2500, 7500) every 2 weeks for 10 weeks. The study showed a lack of clinical benefit in inducing remission over 12 weeks, and there was also a high remission rate in the placebo arm at 42.9% compared with 38.5%, 35.2%, and 47.2% for the 3 doses of TSO.

Two other studies were completed in 2015, but the results have not yet been presented (at the time of this review, clinicaltrials.gov). The first examined 16 patients with left-sided ulcerative colitis after receiving TSO (7500 every 2 weeks for 10 weeks) as compared with placebo. This study was terminated because of the manufacturer’s decision to discontinue TSO production. The MUCUS study is a crossover RCT (in one arm, patients received TSO biweekly for 12 weeks followed by placebo for 12 weeks, whereas in the other arm, patients were assigned to placebo first, then to TSO) assessing mucosal and molecular changes, lymphocyte populations, and gene expression.

The only study that examined non-*T. suis* helmints was a small pilot study with the hookworm, *N. americanus*, in Crohn’s disease. In this study, 9 patients and 3 healthy reservoir donors had a single subcutaneous inoculation of 25 to 50 worm larvae; 5 patients were reinoculated during weeks 27 through 30. Patients displayed some improvement in CDAI at week 20, and 5 were in remission by week 45. However, 2 patients out of those reinoculated had reactivation of their disease. Reported side effects include mild itching, pruritus, painful enteropathy, and mild eosinophilia.

Assessment of helmints in IBD has not recapitulated the findings in animal models, and yet, to date, there appears to be no safety concerns, and disease in some patients treated with TSO was improved. A lack of more impressive, statistically significant suppression of IBD could be due to enrollment of “all comers” and stratification of patients by immuno/genotype may identify patients most suited to helmint therapy. Additional trials are warranted, and also the consideration of other helmint species.
The Use of Helminth-Derived Products to Treat IBD

As an alternative to live larvae or infective ova, the literature is replete with examples of helminth-derived crude extracts or mixed antigen preparations that suppress immune cell activity in vitro and an increasing number of reports that systemic administration of these preparations can block murine colitis95–97 (Table 3). This approach negates any concerns with delivery of a live parasite and tenders the possibility of helminth-derived immunomodulatory molecules as blueprints for novel anti-inflammatory drugs. It is not feasible here to do justice to all the studies in this area; rather, we provide 5 specific examples.

Schistosoma Soluble Egg Antigen (SEA)

S. mansoni infection represents one of the main global health problems in regard to parasites. An array of immunomodulatory properties has been attributed to S. mansoni egg antigens, rather than adult parasites.110 For example, the canonical Th2

<p>| TABLE 2. Summary of Available Clinical Trials for Helminth Therapy in IBDs |
|--------|----------------|-----------------|----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Patients</th>
<th>Study Design</th>
<th>Intervention</th>
<th>Primary Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 7 refractory IBD: 4 CD, 3 UC</td>
<td>Open label</td>
<td>Single-dose 2500 TSO orally</td>
<td>Safety, disease activity, and quality of life (as above)</td>
<td>3/4 CD and all patients with UC achieved remission in 12 wks</td>
</tr>
<tr>
<td>n = 4: 2 CD, 2 UC</td>
<td>Open label</td>
<td>Triweekly dose of 2500 TSO, 30 wk</td>
<td>Safety and efficacy of T. suis therapy</td>
<td>1 patient with CD had a response; others had sustained remission &gt;1 yr</td>
</tr>
<tr>
<td>n = 29 moderate CD</td>
<td>Open label</td>
<td>Triweekly dose of 2500 TSO, 24 wk</td>
<td>Safety and efficacy of T. suis therapy</td>
<td>At week 24: 79.3% response, 72.4% remission; no side effects</td>
</tr>
<tr>
<td>Randomized, double-blind, placebo control</td>
<td>Biweekly dose of 2500 TSO, 12 wks</td>
<td>Clinical response</td>
<td>43.3% response to TSO versus 16.7% to placebo No difference in remission</td>
<td></td>
</tr>
<tr>
<td>n = 54 active UC</td>
<td>Open label</td>
<td>Single dose of Necator americanus L3 larvae</td>
<td>Safety and effectiveness and establishing reservoir donors</td>
<td>At week 20 average CDAI and IBDQ improved.</td>
</tr>
<tr>
<td>n = 9 CD (5 received repeated dose)</td>
<td>(repeated dose at weeks 27–30)</td>
<td></td>
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<tr>
<td>n = 3 healthy</td>
<td>Randomized, double-blind, placebo control</td>
<td>Single-dose 500, 2500, 7500 TSO or placebo</td>
<td>Safety and tolerability of single and escalating dose</td>
<td>General symptoms improved, best in 2500 and 7500 group, and mild side effects</td>
</tr>
<tr>
<td>n = 36 mild-to-moderate CD</td>
<td>Randomized, double-blind, placebo control</td>
<td>Biweekly doses of 7500 TSO (n = 125) or placebo</td>
<td>Improving response (=100 point decrease in CDAI)</td>
<td>No difference in response with TSO versus placebo; nonsignificant improvement with CDAI &gt;290</td>
</tr>
<tr>
<td>n = 250 mild-to-moderate CD</td>
<td>Randomized, double-blind, placebo control; 12-wk open label extension</td>
<td>Biweekly doses of 7500 TSO for 10 wk</td>
<td>Clinical remission at week 12</td>
<td>TSO doses not better than placebo</td>
</tr>
<tr>
<td>n = 252 mild-to-moderate CD</td>
<td>Randomized, double-blind, placebo control, phase 2</td>
<td>Biweekly doses of 250, 2500, 7500 TSO for 10 wk</td>
<td>Clinical response at week 12</td>
<td>Outcome data not available</td>
</tr>
<tr>
<td>n = 16 left-side UC</td>
<td>Randomized, double-blind, placebo control, phase 2</td>
<td>Biweekly doses of 7500 TSO, then wk placebo. Arm 2: reverse of arm 1</td>
<td>Immunological parameters, mucus, microbiota composition</td>
<td></td>
</tr>
<tr>
<td>n = ? UC</td>
<td>Randomized, crossover, double-blind placebo control</td>
<td>Arm 1: Biweekly 2500 TSO 12 wks, then wk placebo. Arm 2: reverse of arm 1</td>
<td></td>
<td></td>
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<tr>
<td>CD, Crohn’s disease; UC, ulcerative colitis; wk, week; yr, year.</td>
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</table>

CD, Crohn’s disease; UC, ulcerative colitis; wk, week; yr, year.
response in murine infection arises only when *S. mansoni* worms shed eggs.\textsuperscript{111} *S. mansoni* experimental infection was among the first models used to test the hygiene hypothesis. Elliott et al. demonstrated that mice injected with freeze/thaw-killed Schistosoma eggs protected against trinitrobenzene sulfonic acid (TNBS)-induced colitis by skewing the immune response toward a Th2-dominant profile.\textsuperscript{43} Intriguingly, injection of a higher number of *S. mansoni* eggs did not offer any protective effect over DSS-colitis; however, in this case, the eggs were delivered intact to the recipient mice,\textsuperscript{49} unlike the previous study where they were freeze/thaw-killed which most likely released antigens. A potent anticolitic effect of *S. mansoni* egg antigens (SEA) was shown in chemical-induced (i.e., DSS) or immune-mediated colitis\textsuperscript{108} and down-regulating numbers of Foxp3\textsuperscript{T} Tregs\textsuperscript{108} and down-regulating IL-17A–producing T cells, respectively.\textsuperscript{112} A strong anticolitic ability is observed with soluble adult worm antigens (SmSWP) in several models of colitis.\textsuperscript{99,107} An important role for genetic factors has also to be taken into account as SEA did not protect out-bred NMRI mice against DSS colitis, whereas live infection significantly reduced signs of disease.\textsuperscript{44} This finding complements our speculation that clinical trials of helminth therapy may need to be conducted with defined patient cohorts.

**Brugia malayi Purified Synthetase**

The nematode *B. malayi* is a major cause of human filariasis. Mice experimentally infected with *B. malayi* recruit immunosuppressive macrophages to the site of infection.\textsuperscript{113} Several dominant antigens have been described in excretory/secretory (E/S) products from *B. malayi*, but their anti-inflammatory properties have not been tested.\textsuperscript{114,115} Recently, a secreted enzyme

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**TABLE 3. Helminth-derived Molecules (Extracts) Can Reduce Enteric Inflammation**

<table>
<thead>
<tr>
<th>Species</th>
<th>Product</th>
<th>Effect of Product</th>
<th>Proposed Mechanism</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nematodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Acanthocheilonema viteae</em></td>
<td>Recombinant cystatin (Av cystatin)</td>
<td>Reduced DSS-colitis</td>
<td>Induction of regulatory macrophages</td>
<td>98</td>
</tr>
<tr>
<td><em>Ancylostoma caninum</em></td>
<td>ES antigens</td>
<td>Reduced TNBS-colitis</td>
<td>Reduced MPO in colon</td>
<td>99</td>
</tr>
<tr>
<td><em>Ancylostoma ceylanicum</em></td>
<td>Adult worm ES and crude antigens</td>
<td>Reduced DSS-colitis</td>
<td>Reduced colonic IFNγ and IL-17</td>
<td>100</td>
</tr>
<tr>
<td><em>Brugia malayi</em></td>
<td>Recombinant asparaginyl-tRNA synthetase (AsnRS)</td>
<td>Reduced T cell–mediated colitis</td>
<td>Reduced IFNγ and IL-17 in spleen, MLN and lamina propria. Increased IL-4 and IL-10</td>
<td>101</td>
</tr>
<tr>
<td><em>Trichinella spiralis</em></td>
<td>tRNA synthetase (AsnRS), secretions from larva</td>
<td>Reduced DNBS-colitis</td>
<td>Reduced colonic MPO, NO, and IL-1β and increased IL-13 and TGFβ</td>
<td>102</td>
</tr>
<tr>
<td></td>
<td>Adult worm secretions</td>
<td>Reduced DSS-colitis</td>
<td>Reduced IFNγ, IL-6, and IL-17 in spleen, MLN, and colonic samples. Increased IL-4, IL-13, IL-10 and TGFβ</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td>Recombinant larvae 53 kDa glycoprotein (TsP53)</td>
<td>Reduced TNBS-colitis</td>
<td>Lower serum levels of TNFα and IFNγ. Increased Arg1, Fizz1, IL-10, and TGFβ</td>
<td>104</td>
</tr>
<tr>
<td><strong>Trematodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Clonorchis sinensis</em></td>
<td>Recombinant type-I cystatin</td>
<td>Reduced DSS-colitis</td>
<td>Induction of IL-10 producing macrophages</td>
<td>105</td>
</tr>
<tr>
<td><em>Schistosoma mansoni</em></td>
<td>Soluble adult worm antigens</td>
<td>Reduced TNBS-colitis</td>
<td>Reduced proinflammatory cytokines in colon and MLN, increased IL-10 and TGFβ</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td>Soluble egg antigens</td>
<td>Reduced T cell–mediated colitis</td>
<td>Reduced IL-17 producing cells and increased IL-4 producing cells</td>
<td>107</td>
</tr>
<tr>
<td></td>
<td>Egg antigens</td>
<td>Attenuated DSS colitis</td>
<td>Reduced IFNγ. Increased IL-10 and Foxp3\textsuperscript{T} cells in colon</td>
<td>108</td>
</tr>
<tr>
<td><strong>Cestodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Hymenolepis diminuta</em></td>
<td>Adult worm extract</td>
<td>Decreased severity of DNBS-induced colitis</td>
<td>Reduced TNFα levels</td>
<td>97</td>
</tr>
<tr>
<td><em>Echinococcus granulosus</em></td>
<td>Laminated layer crude extract</td>
<td>Attenuated DSS colitis</td>
<td>Reduced iNOS expression in colon and NO in plasma</td>
<td>109</td>
</tr>
</tbody>
</table>

E/S, excreted/secreted; FoxP3, forkhead box P3; IL, interleukin; iNOS, inducible nitric oxide synthase; L3, stage 3 larvae; MPO, myeloperoxidase; NO, nitric oxide; TGF, transforming growth factor; TNF, tumor necrosis factor.
from *B. malayi*, asparaginyl-RNA synthetase, was shown to block T cell–dependent colitis in RAG-1–deficient mice.101

**Trichinella spiralis Antigens**

The nematode *T. spiralis* is a zoonotic parasite acquired by humans who consume infected undercooked meat (larvae encyst in muscles); however, most infections in humans are asymptomatic, and this ability of the parasite to go “unnoticed” may be due to secretions from the larvae that can elicit Th2 and Treg responses.116 Excretory/secretory products from *T. spiralis* muscle larvae given intrarectally attenuated macroscopic and histopathological signs of DNBS-induced colitis that was accompanied by reduced colonic levels of myeloperoxidase, nitric oxide (NO) and IL-1β.102 Subsequently E/S products from adult worms were shown to block DSS-induced colitis. Injection (ip.) of the E/S products resulted in less macroscopic disease; lower numbers of IFNγ–, IL-6–, and IL-17–positive cells in the spleen, mesenteric lymph node (MLN), and colon; increases in Th2-type and regulatory cytokines (i.e., IL-4, IL-13, IL-10, and TGFβ) in these locations; and a modest, although statistically significant, increase in CD4+Foxp3+ cells in the MLN.103 Thus, secreted molecules from 2 stages of *T. spiralis* can down-regulate Th1 and Th17 responses and promote a Th2/Treg environment.

Excretory/secretory products of *T. spiralis* contain a protein designated as TsP53 (mw, 53 KDa). Recombinant TsP53 administered subcutaneously reduced TNBS-induced colitis that was accompanied by increased expression of markers, indicative of alternatively activated macrophages (AAMs) (i.e., arginase-1, Relmα) along with IL-10 and TGFβ.104

**Echinococcus granulosus Laminated Layer Antigens**

*E. granulosus* is a 3-segment tapeworm of the small intestine of canines. If ingested by humans, the metacestode stage lodges in vital organs (e.g., lung and liver) causing chronic, serious disease.117

Extracts of the outer laminated layers (LL) of the larval stages can suppress mammalian immune cell activity.118 Use of the LL extract in a prophylactic protocol inhibited DSS-induced colitis that was correlated with lower plasma levels of NO and reduced expression of inducible nitric oxide synthase (iNOS) in the colon.109 Analogous to the application of *S. mansoni* in models of colitis, which has advanced knowledge of how infection with helminths can suppress disease but would not be considered for therapeutic use (this trematode causes sphenomegalgy, liver pathology, and can be fatal), assessment of *E. granulosus* illustrates that specific molecules from parasites that can cause significant human disease could be applied to the treatment of IBD. Analysis of diverse host–parasite interactions can yield data that may translate to novel approaches to human disease.

**Acanthocheilonema vitae Recombinant Cystatin**

*A. vitae* is a filarial nematode of rodents used as a model to understand human lariasis (e.g., elephantiasis). A secreted cystatin from *A. vitae* has been cloned and expressed in *E. coli* systems, and intraperitoneal injection of the purified recombinant cystatin (Av17) has been shown to inhibit DSS-induced colitis.119 Mechanistically, the cystatin elicited a population of regulatory macrophages characterized by argiinase-1 and programmed death ligands 1 and 2 (PD-L1, PD-L2) expression, which evoked T-cell production of IL-10 when added to DC–T cell cocultures. Adoptive transfer of the Av17-evoked macrophages 1 day after the initiation of a DSS-regimen reduced the severity of the colitis, with the transferred cells accumulating in the colon, MLN and spleen.98 A similar regulatory macrophage was first identified by experimental peritoneal infection of mice with *T. crassiceps*. Most likely driven by glycans from the tapeworm, the regulatory macrophages expressed AAM markers (arginase-1, Ym1, and Relmα), and PD-L1 and PD-L2 and were capable of suppressing anti-CD3/anti-CD28 in vitro activation of T cells.120

Thus, as a general comment, a variety of helminth-derived extracts or pure molecules can block the production of proinflammatory mediators, presumably through the activity of IL-10 and/or TGFβ, and mobilize regulatory macrophages, which may have programming distinct from that of the classical IL-4–induced AAMs.

The concerns with helminth antigen therapy are 3-fold. First, as with any treatment, side effects need to be considered and to date, this has not been a feature of studies showing anticolitic effects of helminth-derived molecules. Second, immunogenicity could be problematic if helminth-derived molecules (particularly proteins) lead to host antibody production, which could reduce the efficacy of subsequent treatments. Third, drug development requires purified single molecules, and this is a major caveat of the use of helminth extracts/mixed antigens.121 To date, few pure helminth-derived immunomodulatory molecules have been described and the promise of helminth molecules as drug blueprints remains unfulfilled.122,123 However, this should not deter research in this area because major advances in molecule purification and analytics predict that the structures of helminth-derived immunomodulatory molecules are within reach. As helminth genomes are elucidated,124 the application of bioinformatics may identify structural analogs (agonists or antagonists) of host proteins that impart on the helminth the ability to modify host immunity.125,126

In addition, the possibilities that the anticolitic effect of worm E/S products or crude extracts requires multiple components within the mixture, and that these may be most effective in the context of defined host-derived elements should be entertained. For example, a conditioned medium from macrophages treated with immune serum and E/S products from the nematode *Ascaris suum* elicited maximum healing in an in vitro myofibroblast wound-healing assay.127 Immune complexes can drive AAMs (designated as M2c in 1 classification), and one aspect of anti-TNFα therapy may be the induction of regulatory macrophages.128 The study by Harris et al127 elegantly demonstrates how the immune response against the worm (e.g., antibody synthesis) and the helminth can cooperate to enhance tissue repair and promote an immunoregulatory environment. We speculate that administration of worm products, mixed or purified, as an adjunct therapy could enhance the effectiveness of anti-TNFα in IBD.
Another intriguing and unaddressed area is whether the anti-inflammatory effects of helminth-derived extracts/antigens are mediated, to any degree, by direct or indirect modulation of the composition or activity of the gut microbiota.

**Cellular Immunotherapy in IBD**

Cell-based therapy has been explored as a treatment of Crohn’s disease, with mixed results. Although clinical studies and phase-I/II clinical trials demonstrate that hematopoietic stem cell therapy can induce sustained clinical remission in patients with refractory Crohn’s disease,129–132 a recent phase-III trial revealed no additional benefit of hematopoietic stem cell treatment beyond conventional therapy. Given the many serious adverse events associated with hematopoietic stem cells, as this treatment requires ablation of recipient immune cells, these findings cast doubt on the future of this therapy.133 The outcome of transplantation of mesenchymal stem cells for refractory Crohn’s disease has been mixed,134–136 but may prove efficacious in the treatment of fistulating disease.137–140 Several clinical studies have reported the feasibility of ex vivo-induced Treg cell therapy, and they have shown promise as a treatment of refractory Crohn’s disease.141,142

Given the characterization of regulatory cells induced by helminths and their antigens, the development of helminth-based cell treatments is a third approach and natural extension of the paradigm of helminth therapy. Proof-of-concept using the adoptive transfer of cells retrieved from helminth-infected mice has been illustrated in a variety of murine models of colitis (Table 4). Adaptive transfer of DCs from the MLN and intestine of *H. polygyrus*-infected mice significantly reduced disease in the RAG1−/−IL-10−/− T-cell transfer model of colitis.143 Regulatory B cells from the spleen of *H. diminuta* infected mice inhibited DNSS-, DSS- and oxazolone-induced colitis in recipients, and blockade of DNSS-induced colitis was by a macrophage-dependent, T cell-independent process.52 It is important to note that Treg activity can be mobilized after helminth infection. To wit, the adoptive transfer of Foxp3+ T cells isolated from the MLN or colonic mucosa of *H. polygyrus* infected, but not uninfected, mice, inhibited colitis in the RAG−/−CD4−CD25− T-cell transfer model by means of IL-10.144 Finally, as noted above, adoptive transfer of peritoneal macrophages from mice treated with *A. viteae* cystatin protects against DSS-induced colitis.98 Although instructive, these studies all suffer from a practical limitation—therapeutically, it is less feasible to extract regulatory cells from helminth-infected individuals for the treatment of patients with IBD.

Extrapolating from these studies, one can propose that cells educated in vitro by Th2 cytokines (i.e., those evoked in response to helminths) or worm antigens elicit a cell phenotype that could be used to treat IBD. This autologous therapy would overcome any histocompatibility issues, as a patient’s own cells could be differentiated to a regulatory phenotype and cryopreserved for use on disease reactivation, representing a personalized, precision therapy.

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**TABLE 4. Cytokine, Helminth-educated and Helminth Antigen Cell-based Therapy in Murine Models of Colitis**

<table>
<thead>
<tr>
<th>Cell Source</th>
<th>Disease Model</th>
<th>Effects of Cell Transfer in Recipients</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCs from the MLN and intestine of <em>H. polygyrus</em>-infected mice</td>
<td>IL-10−/− T-cell transfer to RAG KO mice, treated with piroxicam</td>
<td>Reduced microscopic damage score; Foxp3+ from infected mice did not suppress disease.</td>
<td>143</td>
</tr>
<tr>
<td>F4/80+MR+ (AAM) peritoneal cells from <em>T. crassiceps</em>-infected mice</td>
<td>DSS</td>
<td>Reduced colonic shortening and bloody diarrhea, less mucosal histopathology; treatment effect blocked by indomethacin; AAMs reduced proliferation of CD4+ and CD8+ splenocytes in vitro.</td>
<td>47</td>
</tr>
<tr>
<td>IL-4 induced AAMs from bone marrow</td>
<td>DNBS</td>
<td>Suppression of clinical and histological disease scores. Suppression dependent on AAM-derived IL-10, independent of recipient T and B cells and peritoneal macrophages, donor AAMs can localize to colon through β7 integrin.</td>
<td>65,66,144</td>
</tr>
<tr>
<td>Splenic B cells from <em>H. diminuta</em> infected mice</td>
<td>DNBS, DSS, and oxazolone</td>
<td>Reduced clinical and histological disease scores. Suppression dependent on recipient macrophages and independent of T and B cells, reduced colonic IL-1β and IL-17 mRNA and splenic IFNγ, increased splenic IL-4, IL-10.</td>
<td>52</td>
</tr>
<tr>
<td>Colonic or MLN Foxp3+ cells from <em>H. polygyrus</em> infected mice</td>
<td>CD4+CD25− T-cell transfer to RAG KO mice, with piroxicam treatment</td>
<td>Disease suppression, dependent on IL-10 production by transferred cells.</td>
<td>145</td>
</tr>
<tr>
<td><em>H. diminuta</em> antigen treated BMDCs</td>
<td>DNBS</td>
<td>Reduced macroscopic and histopathology damage scores, enhanced splenic IL-4 and IL-10; suppression of disease dependent on recipient adaptive immunity and IL-10.</td>
<td>146</td>
</tr>
</tbody>
</table>

BMDC, bone marrow-derived DCs.
medicine approach to IBD. Both scenarios have been explored in animal models. The potential for macrophages to treat inflammatory disease has received significant attention in this context; macrophages exposed to IL-4, whether fresh or cryopreserved, inhibit DNBS- and oxazolone-induced colitis. Intriguingly, exposure to tegumental antigens, peroxiredoxin, or fatty acid–binding protein from the trematode Fasciola hepatica elicits a regulatory AAM phenotype in mouse cells; these cells have not been tested for any anticolitic capacity.

DCs are attractive candidates for a cell-based therapy. They are readily and easily differentiated from blood monocytes, are highly migratory, and can drive potent adaptive immune responses. Autologous DCs have been used as a cell-based therapy to enhance immunogenicity toward tumors in patients with non-Hodgkin’s lymphoma, melanoma, and colorectal, lung, and prostate cancer. Bone marrow–derived DCs treated with a crude extract of H. diminuta significantly suppressed DNBS-induced colitis in recipient mice. The anticolitic effect was mediated by adaptive immunity and IL-10 in the recipient, and the antigen-pulsed DCs induced an IL-10 producing splenic CD4+ T cell that could similarly suppress colitis in recipient mice. Likewise, an extract of the tegument of F. hepatica, in concert with the TLR9 agonist CpG, elicits a bone marrow–derived DC which, via CD4+CD25+Foxp3+ T cells, can reduce arthritis in recipient mice. Corroborating these helminth-based studies, adoptive transfer of bone marrow–derived DCs treated in vitro with vasoactive intestinal peptide or lactobacillus can inhibit TNBS-induced colitis, in both instances through CD4+ T cells.

An inherent advantage in this adaptation of helminth therapy is that the patient is not exposed to viable parasites or even worm products, only their own cells programmed in vitro to be anticolitic by exposure to worm extracts/antigens. This also overcomes the significant challenge of identifying pure worm molecules for drug development. However, the potential for malignancy when using a patient’s re-programmed cells should not be overlooked. Thus, while the study of helminth-based cellular therapy is in its infancy, data from animal models are encouraging and the translational potential of this therapeutic modality may be worthy of consideration in the treatment of IBD.

CONCLUSIONS

IBD takes a terrible toll on the life of patients and their caregivers; the etiology of IBD is diverse and as the incidence of these diabolical conditions increase better therapies and cures are urgently needed. Infection with helminth parasites is a potent stimulus and modifier of the mammalian immune system, as the host seeks to eliminate the parasite and the helminth endeavors to undermine the host’s attempt to eradicate it. Intuitively, one can accept that immune events subsequent to infection would affect the severity of concomitant disease in the host. Data from animal (mainly rodent) models almost uniformly, and overwhelmingly, support helminth therapy for a range of autoimmune diseases, whereas those from human studies are more equivocal. Evaluating the data for helminth therapy in IBD, 3 broad and conceptually distinct approaches were presented (Fig. 2); each can blunt or inhibit intestinal inflammation through common or divergent mechanisms, and the latter is important as it could translate to multiple new ways to treat IBD. We contend that analysis of host–parasite interactions will reveal novel approaches to manipulate immunity and alleviate immunopathology. Prescription of a specific species of helminth may eventually be matched to cohorts of well-characterized patients with homogenous disease. The promise of helminth extracts or E/S products to yield

![FIGURE 2](https://www.ibdjournal.org)
blueprints for new immunomodulatory drugs remains unfulfilled; however, this could be a lucrative area of research. The use of host cells pulsed with helminth antigens/extracts is a novel cellular immunotherapy that may gain traction in the coming years; this personalized approach could be particularly exciting, as a patient’s own cells become their therapy. The boundary between friend and foe in host–parasite relationships may be more gray than black-and-white.

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