

Helminth therapy for organic diseases?



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Autoimmune and chronic inflammatory organic diseases represent a “postindustrial revolution epidemics,” and their frequency has increased dramatically in the last century. Today, it is assumed that the increase in hygiene standards reduced the interactions with helminth parasites that coevolved with the immune system and are crucial for its proper functioning. Several helminths have been proposed and tested in the search of the ideal therapeutic. In this review, the authors summarize the translational and clinical studies and review the caveats and possible solutions for the optimization of helminth therapies. (Translational Research 2015;166:586–601)

Abbreviations: aaMac = alternatively activated macrophage; AR = allergic rhinitis; Arg = arginase; Asc = *A. suum* extracts; CD = Crohn disease; CIA = collagen-induced arthritis; CNS = central nervous system; DC = dendritic cell; DSS = dextran sodium sulfate; E/S = excretory/secretory products; IBD = inflammatory bowel disease; IFN- γ = interferon gamma; IL = interleukin; iNOS = inducible nitric oxide synthase; INS-GAS = male insulin gastrin; MIF = macrophage inhibitory factor; MOG = myelin oligodendrocyte glycoprotein; MR = mannose receptor; NKT = natural killer T cell; NO = nitric oxide; OVA = ovalbumin; PC = phosphorylcholine; RA = rheumatoid arthritis; STZ = streptozotocin; Th = T-helper cell; TLR = toll-like receptor; TNF = tumor necrosis factor; Treg = regulatory T cells; TSO = *T. suis* ova; UC = ulcerative colitis; TGF = transforming growth factor; CXCL = chemokine (C-X-C motif) ligand; MCP = monocyte chemoattractant protein; MS = multiple sclerosis; STAT6 = signal transducer and activator of transcription 6; MRI = magnetic resonance imaging; BALB/C = inbred mouse strain; TNBS = 2,4,6-trinitrobenzenesulfonic acid; SPF = specific pathogen free; ILC = innate lymphoid cells; CKBP = chemokine binding protein; K/BxN = mice expressing the KRN T cell receptor transgene and the MHC class II molecule Ag7; NF- κ B = nuclear factor kappa B; DBA = mouse strain; MIP = Macrophage inflammatory protein; RANTES = regulated on activation, normal T cell expressed and secreted; UC = ulcerative colitis; SCCAI = simple clinical colitis activity index; PBMC = peripheral blood mononuclear cells; HLA-DR = human leukocyte antigen DR

HYGIENE AND THE “OLD FRIENDS” HYPOTHESIS

In the early years of the 19th century, industrialization led to a substantial improvement of the health system. At the same time, industrializing countries experienced a constant rise in the incidence of immunorelated disorders.¹ These disorders share a complex etiology and several genetic risk loci (Table I), suggesting a common etiology. The hygiene hypothesis suggests that modern hygienic standards reduced the exposure to stimuli that can prevent or reduce the

severity of these disorders.² In particular, hygiene leads to the partial deprivation of microbial “old friends” that were previously abundant and shaped the evolution of the human immune system. Helminths are obvious “old friends candidates” that cause chronic carrier states or nonfatal subclinical diseases and need a customized immune response.

Two groups of helminths evolved zoo parasitism and were present during key periods in the evolution of the vertebrate immune system (Fig 1).^{3,4} Platyhelminthes

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Table I. IBD risk loci shared with other immunorelated diseases

Disease	# Overlapping loci	Fold enrichment	Enrichment OR	95% CI	P value
Psoriasis	14	13.5	14.71	8.50–25.45	4.15×10^{-12}
Atopic dermatitis	3	12.1	12.32	3.93–38.62	2.05×10^{-3}
Rheumatoid arthritis	12	10.92	11.74	6.52–21.14	1.64×10^{-9}
Celiac disease	16	10.57	11.64	6.95–19.51	4.56×10^{-12}
Type 1 diabetes	20	9.99	11.28	7.06–19.03	2.35×10^{-14}
Multiple sclerosis	17	8.19	9.06	5.48–14.97	5.11×10^{-11}
Asthma	7	7.61	7.91	3.71–16.88	4.90×10^{-5}

Abbreviations: CI, confidence interval; IBD, inflammatory bowel disease; OR, odd ratios.
Adapted from: Jostins et al.¹³⁰

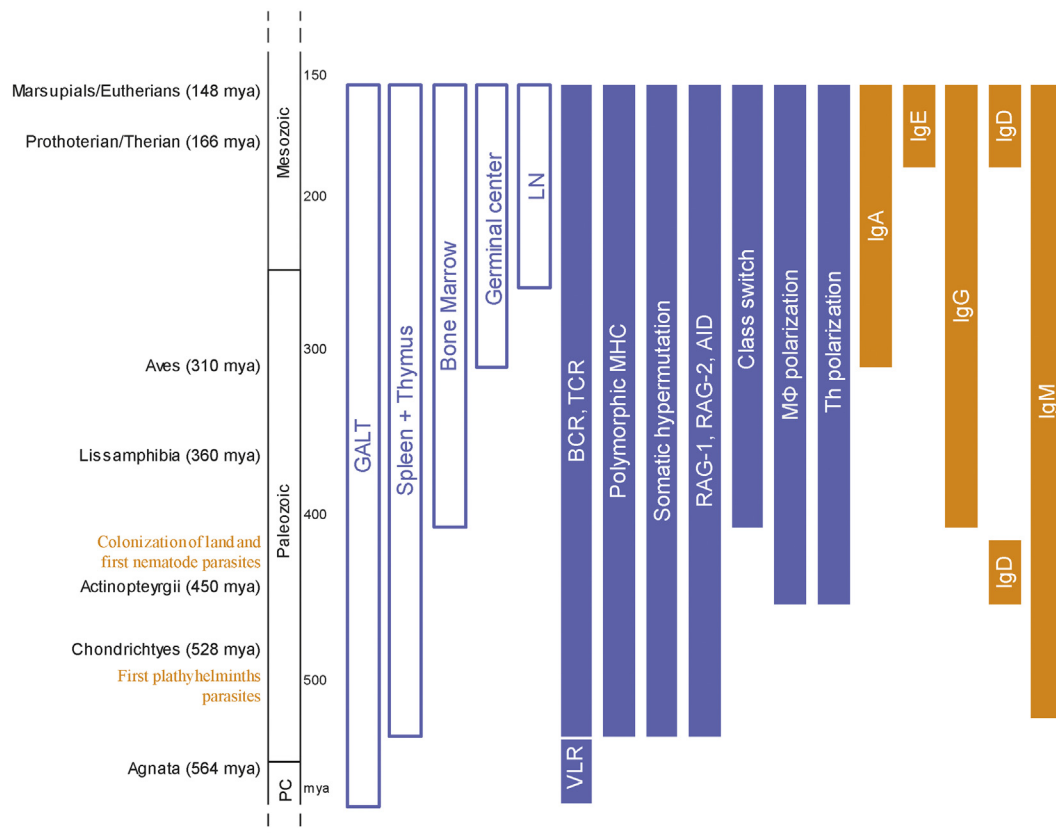


Fig 1. Milestones of the immune system evolution in vertebrates occurred in presence helminth parasites. AID, activation-induced cytidine deaminase; BCR, B cell receptor; GALT, Gut-associated lymphoid tissues; IgE, immunoglobulin E; LN, lymph nodes; MHC, major histocompatibility complex; PC, Precambrian; RAG, Recombination-activating gene; TCR, T-cell receptor; VLR, variable lymphocyte receptors. Adapted from Rook⁵ and Litman et al.³

parasitism probably arose from a common parasitic ancestor in the first jawed fishes, whereas nematodes parasitism emerged independently at least 5 times in terrestrial vertebrates.⁵ Helminths exerted a strong pressure on their host genome,⁶ which led to the coevolution of an intricate host–parasite relationship where

helminths assumed an essential role in the development of tolerance and immunoregulatory pathways.⁵ The evolution of the T helper 2 (Th2) and regulatory T cells (Treg) subsets favors the persistence of the pathogen inside the host, avoids a destructive inflammatory response, and ensures a constant antigen source and

immune stimulus, resulting in striking immunity to reinfection.⁷ A further milestone is the development of different macrophage phenotypes that are often encountered on chronic infections.^{8,9} Type 2 cytokines drive the polarization of alternatively activated macrophages (aaMacs) that secrete the anti-inflammatory interleukin (IL)-10 and TGF- β and contribute to extracellular matrix repair, wound healing, and fibrosis.¹⁰

THE “IDEAL THERAPEUTIC HELMINTH”

Key for the survival of a helminth in the host is the expulsion of waste products and the secretion of molecules involved in immune evasion, extra corporal digestion, and molting. Molecules excreted and secreted by helminths are collectively termed “excretory/secretory products (E/S) products.” Different helminth parasites have a considerable variety in the interaction with the immune system that could be therapeutically used to counteract an aberrant immune response. An “ideal therapeutic helminth” should have—besides the essential immune-modulatory potential—a limited pathogenicity in the human host and a simple life cycle with no dissemination (Table II).^{11,12} The infection should be nonproductive inside humans to ensure a control over the amplitude of the immunomodulation. In case of complications, it is important that the parasite can be easily eradicated using standard antihelminthic drugs. Importantly, the possibility of production in a specific pathogen-free environment is needed to avoid eventual coinfections.

ALLERGY

In 1970, Preston¹³ noted that patients suffering from hay fever entered remission following *Ascaris* infection and suggested that the lack of infection could lead to atopic syndrome. Later, Jarrett et al¹⁴ noted that in rats infected with *Nippostrongylus brasiliensis*, subsequent systemic anaphylaxis and skin test reaction were strongly reduced. Confirming these observations, patients infected with different parasitic species were barely affected by passive skin sensitization.¹⁵ To date, several mouse studies have shown a protective effect of helminths in allergy models, especially when administered at sensitization. In a model of peanut food allergy, infection with *Heligmosomoides polygyrus* has an IL-10 dependent preventive effect. Administration of *H. polygyrus* E/S products at sensitization reduces the type 2 response at challenge in both fungal allergen and ovalbumin (OVA)/alum-induced airways inflammation by suppressing the activation of group 2 innate lymphoid cells and their production of type 2 cytokines.^{16,17} In contrast, the heat-sensitive E/S

Table II. The ideal therapeutic helminth

No dissemination
Not pathogenic to human
Self-limited infection
No replication inside the host
Not immediately infective
Easy administration
Effective anthelmintic available
Production in SPF conditions possible
Long-term stability

Adapted from Elliot et al.¹²

component suppresses eosinophils recruitment without influencing the type 2 response.¹⁸

IL-10 appears essential in the prevention of OVA-induced lung inflammation by *N. brasiliensis*¹⁹ and in the protection from systemic fatal anaphylaxis by *Schistosoma mansoni*, where an increase in IL-10-producing B cells inhibits the IL-4 response.²⁰ *Schistosoma* produce chemokine-binding proteins that bind CXCL8 and reduce neutrophil infiltration in asthma and contact hypersensitivity models.²¹ The important role of IL-10 is supported by studies with a cystatin derived from the filarial helminth *Acanthocheilonema vitae* that suppresses both OVA- and grass-pollen-induced airways inflammation via induction of IL-10 producing macrophages.^{22,23} Cystatin administration also decreases eotaxin-1, eotaxin-3, and MCP-1 expression in the lung tissues.²⁴ Another filarial product, the glycoprotein ES-62, protects from OVA-induced inflammation by reducing Th2 and Th17 responses and inducing Th1 responses.²⁵ The phosphorylcholine (PC) modification decorating ES-62 was used as a template to design small immunomodulatory analogs.²⁶ Two of these molecules, 11a and 12b, inhibit mast cell degranulation and cytokine production and prevent OVA-induced airway inflammation and eosinophil infiltration in the lungs.²⁷ The protective effects of *Oesophagostomum dentatum* extracts in a birch pollen allergy model and of *Trichuris suis* products in the OVA model further confirm that an infection with live parasites is not essential for the prevention of allergy development.^{28,29} These and other studies demonstrate the protective effect of helminths against the development of allergies; yet, whether helminths improve an already established allergy is less clear. *N. brasiliensis* infection in sensitized rats does not prevent a subsequent hypersensitivity response³⁰ and fails to protect mice from an established OVA allergy and from OVA anaphylaxis.¹⁹

In contrast, *Strongyloides venezuelensis* infection after an OVA challenge protects rats against a later hypersensitivity response.³¹ A therapeutic effect is also exerted by *H. polygyrus* in OVA-sensitized mice.³² Finally,

Table III. Summary of the studies on the therapeutic use of helminth infection or helminth-derived products in rodent model of different organic diseases

Author	Mechanisms	Species	Parasite	Disease models
Asthma/allergy Schnoeller et al ²² ; Danilowicz-Luebert et al ²³ ; Rzepecka et al ^{25,27}	Cystatin affects Macs (IL-10 dep), ↓Th2, mast cell degranulation. oligoprotein ES-62: ↓Th1, Th2, eosinophils, and neutrophils infiltration	Mouse	<i>Acanthocheilonema</i> (Nematode)	OVA-airway allergy; grass pollen–airway allergy
Ji et al ²⁴	Cystatin: ↓eotaxin-1, eotaxin-3, MCP-1 (lung); ↓Th2 CKs, IL-17A, OVA-specific IgE; ↑IL-10 levels (serum)	Rat	<i>Angiostrongylus</i> (Nematode)	OVA-airway allergy
Cho et al ³³	MIF signals via TLR2 on lung EC. ↑IL-10 by Treg	Mouse	<i>Anisakis</i> (Nematode)	OVA-airway allergy
Bashir et al ¹³¹ ; Wilson et al ³² ; Kitagaki et al ¹³² ; McSorley et al ¹⁷	↓Ag-specific IgE, IL-13 by Ag-specific T cells. ↑TGFβ, IL-10 by Treg. IL-33 blockade, ↓ILC2	Mouse	<i>Heligmosomoides</i> (Nematode)	Peanut-allergy model, OVA-airway allergy
Wohlleben ¹⁹	Ag-specific IgG1 and IgE. IL-10 dep	Mouse	<i>Nippostrongylus</i> (Nematode)	OVA-airway allergy
Mangan et al ²⁰ ; Smith et al ¹⁰⁵	IL-10–producing B cells; CKBP: ↓CXCL8-induced neutrophil infiltration and inflammation	Mouse	<i>Schistosome</i> (Trematode)	Systemic fatal anaphylaxis, air pouch; contact hypersensitivity
Rzepecka et al ²⁵	Restore Th1/Th2 balance, ↓Th1	Mouse	<i>Trichuris</i> (Nematode)	OVA-airway allergy
Multiple sclerosis Walsh et al ⁴²	↓Auto-Ag–specific Th1 and Th17 (TGF-β dep). DC induces parasite-specific IL-10 ⁺ TGF-β ⁺ Treg cells	Mouse	<i>Fasciola</i> (Trematode)	EAE
Sewell et al ³⁹	↑Th2 shift (STAT6 dep, LNFPIII sufficient), ↑IL-10 and TGF-β.	Mouse	<i>Schistosome</i> (Trematode)	EAE
Reyes et al ⁴³	↓Ag-specific splenocyte proliferation, ↓IL-17, TNF-α. ↑IL-4, IL-10, ↓leukocyte CNS infiltration	Mouse	<i>Taenia</i> (Cestode)	EAE
Rheumatoid arthritis Rocha et al ⁵⁹	↓NO, ↓IL-1β, IL-10 (not in CIA)	Rat, mouse	<i>Acanthocheilonema</i> (Nematode)	ZYA, CIA
Pineda et al ^{56,57} ; Al-Riyami et al ²⁶	↓IFN-γ and IL-17; ES-62, ↑IL-22; PC moiety: targets IL-17–producing network, (DC γ/δ or CD4 ⁺ T cells signaling). ↓MyD88 and TLRs (by Th17 cells). modulated γ/δ T cells migration (↓CD44), ↓IL-infiltrating cells	Mouse	<i>Anisakis</i> (Nematode)	CIA, K/BxN-induced polyarthritis
Osada et al ^{51,86} ; Song et al ⁵²	↓Anti-CII IgG and IgG2a, ↑anti-CII IgG1 ⁺ ; ↓Splenocyte Ag-mediated proliferation, ↓Th1, Th17; ↓NF-κB; ↑IL-10 by CD4 ⁺ .	Mouse	<i>Schistosome</i> (Trematode)	CIA, spontaneous RA (IL-1Ra KO)
Psoriasis Atochina et al ⁷²	↓Gr1 ⁺ F4/80 ⁺ Macs, ↓CD8 ⁺ T cells	Mouse	<i>Schistosome</i> (Trematode)	Spontaneous psoriasis-like pathology (flaky skin)
Transplant rejection Komine-Aizawa et al ⁷¹	↓IL-4, IL-23, and TNF-α (serum)	Mouse	<i>Dirofilaria</i> (Nematode)	Immune-mediated pregnancy loss (abortion-prone CBA/J × DBA/2J)
Li et al ^{63,67}	↓CD4 ⁺ , CD8 ⁺ , CD28 ⁺ T cells, ↓Fkn mRNA. ↑IL-10 (serum)	Rat	<i>Echinococcus</i> (Cestode)	Orthotopic liver transplantation

(Continued)

Table III. (Continued)

Author	Mechanisms	Species	Parasite	Disease models
Ledingham et al ⁶⁴ ; Liwski et al ⁶⁵ Diabetes	↓CD4 ⁺ and CD8 ⁺ infiltration and proliferation; ↓T-cells cytotoxicity; ↑IL-4 expression (leukocytes)	Rat	<i>Nippostrongylus</i> (Nematode)	Kidney, cardiac allografts
Imai et al ⁷⁵	↓Th1, ↑Th2	Mouse	<i>Dirofilaria</i> (Nematode)	NOD
Lund et al ⁸⁴	↓IFN- γ by auto T cell. IgG2a to IgG1 switch, ↑aaMAcs	Mouse	<i>Fasciola</i> (Trematode)	NOD
Mishra et al ⁸³	CD25, STAT6, IL-10-indep.	Mouse	<i>Heligmosomoides</i> (Nematode)	NOD, STZ
Hubner et al ⁷⁶ ; Larson et al ¹³³	↑Th2, Treg (not essential), ↑insulin-specific IgG1	Mouse	<i>Litomosoides</i> (Nematode)	NOD
Cooke et al ^{74,78,81}	↑Th2, IL-10; ↑C-type lectins; ↑Treg (pancreas, DC and TGF β dep). Dep on CD25 ⁺ T cells. glycoprotein ω -1: ↑Th2 polarizing DCs (TGF β , retinoic acid-dep)	Mouse	<i>Schistosoma</i> (Trematode)	NOD
Gastritis Martin et al ⁹² Fox et al ⁹¹ ; Whary et al ⁹³	↑Anti-inflammatory mediators mRNA (transient) ↓Th1 response; ↑FoxP3 ⁺ T cells	Gerbils Mouse	<i>Brugia</i> (Nematode) <i>Heligmosomoides</i> (Nematode)	<i>H. pylori</i> -induced gastritis <i>H. pylori</i> , <i>H. felis</i> -induced gastritis
Hepatitis Nascimento et al ⁸⁷	↓Cellular infiltration, ↑IL-4, IL-10, and IL-13. ↑Liver fibrosis	Mouse	<i>Ascaris</i> (Nematode)	Concanavalin A-induced autoimmune hepatitis
Colitis Cho et al ¹³⁴	↓Inflammatory CK, ↑Treg, MIF-II: ↑IL-10 by EC, DCs, and fibroblasts and TGF- β by fibroblasts.	Mouse	<i>Anisakis</i> (Nematode)	DSS colitis
Schnoeller et al ²² ; Whelan et al ¹¹⁵	↑Foxp3 ⁺ Tregs, ↓local IL-6 and IL-17 A production, ↓MIP-1 α/β , MCP-1/3, and RANTES, ↓Macs (colon)	Mouse	<i>Acanthocheilonema</i> (Nematode)	DSS colitis
Kron et al ¹¹⁶	Asparaginyl-tRNA synthetase induced IL-10 production from CD3 ⁺	mouse	<i>Brugia</i> (Nematode)	T-cell transfer colitis
Wang et al ¹³⁵ ; Reardon et al ¹⁰⁰ ; Hunter et al ¹⁰¹	↑TGF- β ⁺ CD19 ⁺ splenic follicular B cells. ↑Th2, Treg. aaMac mobilization. Requirement of IL-10 model dep	Mouse	<i>Hymenolepis</i> (Cestode)	DNBS, oxazolone, DSS colitis
Elliott et al, ¹⁰² Zhao et al ¹³⁶ ; Xia et al ¹⁰³ ; Heylen et al ¹³⁷ ; Heylen et al ¹⁰⁴	↓Th1, ↓IL-17 A ⁺ T cells; ↓TLR4 expression; ↑IL-4 ⁺ T cells; ↑TJ proteins. Role of STAT6	Mouse	<i>Schistosoma</i> (Trematode)	T-cells transfer, TNBS colitis
Du et al ¹⁰⁹ ; Motomura et al ¹⁰⁸	↑Th2, Treg, aaMacs	Mouse	<i>Trichinella</i> (Nematode)	DSS, TNBS, DNBS colitis
Elliott et al ¹⁰² ; Setiawan et al ¹³⁸ ; Sutton et al ¹³⁹ ; Hang et al ¹⁴⁰ ; Blum et al ¹⁴¹	↓Th1, ↓IL-17 production; ↓IL12p40 production and CD80, CD86 expression by DC; DC block gut Ag-specific IFN- γ /IL-17 T cell response; ↑Th2, Treg, induction. Protective T cells. IL-10 R signaling.	mouse	<i>Heligmosomoides</i> (Nematode)	IL-10—/—, TNBS, DSS, Ag-driven, IL-10—/— T cell transfer colitis

Abbreviations: aaMacs, alternative activated macrophages; CD, Crohn disease; CIA, collagen-induced arthritis; CK, cytokines; CNS, central nervous system; DC, dendritic cell; EAE, experimentally induced autoimmune encephalomyelitis; EC, epithelial cells; ES, excretory/secretory antigen; DSS, dextran sodium sulfate; IFN, interferon; in/dep, in/dependent; IgE, immunoglobulin E; IL, interleukin; LNFPIII, lacto-N-fucopentaose III; Macs, Macrophages; MIF, macrophage inhibitory factor; NO, nitric oxide; NOD, nonobese diabetic; OVA, ovalbumin; PC, phosphorylcholine; RA, rheumatoid arthritis; STZ, streptozotocin; Th, T-helper cell; TLR, toll-like receptor; TNF, tumor necrosis factor; Treg, regulatory T cells.

Anisakis simplex produces a macrophage inhibitory factor (MIF)-homologue that can suppress airway inflammation in mouse by inducing IL-10 production and Treg recruitment; this effect is strongly dependent on the expression of toll-like receptor (TLR)2 by lung epithelial cells.³³ Two double-blind, placebo-controlled studies were performed in allergic rhinitis (AR) patients using *Necator americanus* larvae^{34,35} or *T. suis* ova (TSO).^{36–38} Yet, both studies failed to provide sufficient evidence on the efficacy and tolerability of this helminth therapy in AR.¹¹ Improved results might derive from a standardization helminth treatment period that should preferably occur before the onset of the pollen season.¹¹

MULTIPLE SCLEROSIS

A treatment with *S. mansoni* ova was the first to be studied in murine experimental autoimmune encephalomyelitis (EAE).³⁹ *S. mansoni* ova treatment decreased the incidence and delayed the onset of EAE in wild-type mice, but not in STAT6-deficient animals. Furthermore, it reduced myelin oligodendrocyte glycoprotein-specific interferon gamma (IFN- γ), nitric oxide, and tumor necrosis factor (TNF) α production.^{39,40} A glycan extracted from the egg of *S. japonicum*, lacto-N-fucopentaose III (LNFPIII), reduces EAE severity and induces a Th2 profile.⁴¹ Similarly, *Fasciola hepatica* promotes tolerogenic dendritic cells (DCs) that induce parasite-specific Treg cells. In turn, Treg produce IL-10 and TGF- β that suppress Th1 and Th17 responses in the central nervous system.⁴² Moreover, *Taenia crassiceps* limits the production of IL-17 and TNF α and the migration of T cells to the central nervous system.⁴³

Clinical studies^{44,45} compared 12 MS patients with a mild, asymptomatic intestinal parasitism with 12 uninfected patients over a period of 7.5 years. The infected MS patients had a better clinical and radiological outcome, associated with the induction of Treg, anti-inflammatory cytokine secretion, and increased expression of TLR2 on B cells and DCs and of CD1d on IL-10-producing B cells. Both the MS protection and the anti-inflammatory pattern reverted in 4 patients receiving antihelminth treatment. No effect on IL-10 was observed on treatment with TSO in 4 secondary progressive MS patient. The patients did not report any clinical benefit but showed a trend toward a reduction of the Th1 responses.^{46,47} In 5 newly diagnosed MS patients, TSO led to a transient reduction of the gadolinium-enhancing MRI lesions that relapsed after TSO withdrawal.⁴⁸ Additionally, a recent study in relapsing mannose receptor showed no benefit on TSO therapy.⁴⁹ Of note, this study did not test the number

of gadolinium-enhancing MRI lesions that was found to be reduced in the previous trial.⁴⁸ Overall, larger, placebo-controlled, long-term studies might help evaluating the benefits of TSO therapy in MS patients.

RHEUMATOID ARTHRITIS

The first correlation between parasite and rheumatoid arthritis was the incidental finding that infection with the *Syphacia oblevata* is protective in male rats.⁵⁰ Other parasite infections led to contrasting outcomes. *Schistosoma* infection reduces the severity of a subsequent collagen-induced arthritis (CIA) but exacerbates an already established CIA.^{51,52} Further, *Hymenolepis diminuta* worsens a subsequent induced polyarthritis,⁵³ whereas *T. crassiceps* infection has no effect on the development of rheumatoid arthritis induced by adoptive OVA-specific T-cell transfer.⁵⁴ The filarial ES-62, effective in allergy models, also reduces the symptoms of CIA. The PC moiety of ES-62 possesses immunomodulatory activity⁵⁵ and targets DC, $\gamma\delta$, and Crohn disease (CD)4⁺ T cells to modulate the IL-17/IL-22 producing network.⁵⁶ The mechanism of action appears to involve the downregulation of the adaptor MyD88 in Th17, mast cells, and macrophages that leads to an inhibition of TLR/IL-1R signaling.^{57,58} An analogue of ES-62 PC moiety (11a) was successfully employed to prevent CIA in mice and caused a downregulation of the IFN- γ and IL-17 responses.²⁶ Similarly to ES-62, an extract from *A. suum* protects against zymosan-induced arthritis in rats and ameliorates CIA in mouse, while reducing the levels of nitric oxide, IL-1 β , and IL-10.⁵⁹

TRANSPLANT REJECTION

BALB/C mice infected with *Trichinella spiralis* larvae 23 days before a skin graft from C57BL/6 donors retain the transplant longer. Timing is crucial, as an infection performed 7 days before transplant has a milder effect.⁶⁰ Injection of a soluble larval extract is sufficient to delay rejection, supporting a role of an E/S product.⁶¹

Echinococcus-infected individuals can develop hepatocellular carcinoma and often require a liver transplant. On transplantation, a milder immunosuppression regimen must be adopted to avoid the exacerbation of the parasitic disease. Despite the milder immunosuppression, the transplants are usually well tolerated and rarely rejected.⁶² This effect has been reported in mouse models of both liver and heart transplants, indicating a systemic effect.⁶³ *N. brasiliensis* or worm extract prolongs the survival of kidney and heart transplants in rat and mouse models and reduces CD8⁺, CD4⁺ lymphocytes. *N. brasiliensis* also diminishes the

allospecific cytotoxicity of spleen lymphocytes and polarizes toward a Th2 response.^{64,65} *Schistosoma* infection prolongs the survival of skin allograft only in mice infected 60 days before the transplant, suggesting a role for the late-phase Th2 response.⁶⁶ Infection of recipients with *H. polygyrus* protects mice from graft vs host disease after a bone marrow transplant by enhancing the protective Treg response.⁶⁷ The mammalian fetus can be seen as a semi allograft within the uterus because it expresses paternal MHC antigens. Women suffering from repeated pregnancy loss have higher IL-17 and IL-23 levels when compared with women with normal pregnancy.⁶⁸ Furthermore, their number of Treg in blood is decreased to nonpregnancy levels.⁶⁹ In a murine model of spontaneous abortion, a filarial polyprotein significantly leads to a 4-time reduction of the fetuses' resorption rate.⁷⁰ Interestingly, this reduction occurs in the absence of a Th2 cytokines' upregulation and is characterized by diminished levels of IL-4, IL-23, and TNF α , whereas IL-17 levels were unchanged.⁷¹

PSORIASIS

Flaky skin BALB/c mice have a spontaneous skin phenotype that closely resembles human psoriasis, and they develop skin lesions as early as the age of 5 weeks. Treatment with LNFPIII prevents the development of skin lesions in 77% of the mice.⁷² LNFPIII signals via TLR4 causing a rapid and transient NF- κ B activation that leads to the activation of DC primed to induce a Th2 phenotype.⁷³

DIABETES

Infecting 5- to 7-week-old nonobese diabetic (NOD) mice with *Schistosoma* reduces the incidence of diabetes (described as blood glucose levels >12 mmol/L).⁷⁴ Diabetes is also prevented by injection of *Schistosoma* eggs in 5-week-old mice, highlighting the importance of the egg-directed Th2 response. As in other models, infection with a viable parasite is not necessary: *Filaria* and *S. mansoni* products injected in 4- to 6-week-old NOD mice completely prevent insulinitis and diabetes development by impairing the anti-islet Th1 cell response.^{75,76} The protective effect is exerted in young mice around the age of 5 weeks, when islet antigens presentation in pancreatic lymph nodes begins gradually causing the infiltration of antigen-presenting cell and lymphocytes.⁷⁷ *S. mansoni* eggs products induce Treg, aaMac, Th2 responses, and increase the numbers of natural killer T cells that are usually reduced in NOD mice.⁷⁸ Presentation of egg-glycoconjugates by DCs to CD1d-restricted cells such as natural killer T cells is important for an adequate

Th2 response.^{79,80} Diabetes in NOD mice is also prevented by injection of the *Schistosoma* egg glycoprotein ω -1 that induces both FoxP3 and IL-4.⁸¹ A preventive Th2 response is also observed in NOD mice infected with *T. spiralis* and *H. polygyrus*.⁸² *H. polygyrus* protection from diabetes also occurs in a Th2-deficient environment through an IL-10-dependent mechanism.⁸³ Instead, *F. hepatica* E/S products suppress the autoantigen-specific production of IFN- γ and increase the numbers of IL-10-secreting B cells and aaMac that might inhibit the initiation of autoreactive T-cell responses.⁸⁴ Several studies have shown protective effect of helminths in NOD mice; yet, their clinical relevance is disputable. Indeed, it is relatively easy to prevent diabetes in NOD mice even with nonspecific interventions.⁸⁵ Another common diabetes model in rodents implies the administration of streptozotocin (STZ), a cytotoxic glucose analog that causes the destruction of β cell. The pathology caused by multiple low doses of STZ is immune mediated and can be reduced by infection with *H. polygyrus*⁸⁶ that protects pancreatic islets and reverses the increase of proinflammatory mediators in a STAT6 and IL-10 independent manner. In contrast, the hyperglycemia induced by single high-dose STZ is immune mechanism independent and is not affected by *H. polygyrus* infection.⁸⁶

AUTOIMMUNE HEPATITIS

Autoimmune hepatitis is a chronic hepatocellular inflammation and necrosis that, if left untreated, might progress to cirrhosis and hepatocellular carcinoma. In the mouse autoimmune hepatitis model, injection of concavallin leads to a massive Th1 lymphocytes activation and infiltration into the liver. Treatment with *A. suum* extracts 30 minutes before concavallin reduces the extent of liver damage, induces a type 2 response, and increases the survival rate from 38% to 100%. Instead, the treatment efficacy is limited if performed 2 hours after concavallin. Unfortunately, *A. suum* extracts exacerbate liver fibrosis, an adverse effect that might limit its clinical use.⁸⁷

COELIAC DISEASE

A small study was performed in 10 coeliac disease patients in remission. In a first double-blinded trial, patients were treated with *N. americanus* larvae.⁸⁸ In a crossover study, 7 of the previously control patients were treated.⁸⁹ Although the symptom severity after gluten challenge remained unchanged, *N. americanus* reduced IFN- γ and IL-17 production by intestinal tissues. A subsequent open-label trial showed that a combination of *N. americanus* and desensitization immunotherapy by microchallenge with deamidated

Table IV. Clinical studies and case reports with TSO and *Trichuris trichiura* ova in IBDs, multiple sclerosis, and allergic rhinitis

Citation	Nematode	Dose and dosage	Baseline medication allowed	n/Placebo	Kind of trial	Severity	Outcome	Adverse effects
IBD								
Summers et al ¹¹⁷	<i>T. suis</i>	2500 TSO	Prednisone, antibiotics, 5-ASA, AZA, 6-Mp	4 CD, 3 UC	Open label	CD (CDAI > 180) and active UC	+week 8: 86% remitted*	No
Summers et al ¹¹⁸	<i>T. suis</i>	2500 TSO every 3 w for 24 w	14/29 on corticosteroids	29/0	Open label	CD (CDAI: 220–450)	+week 12: 75% responded, 65% remitted week 24: 79% responded 72% remitted [†]	No
Summers et al ¹¹⁹	<i>T. suis</i>	2500 TSO every 2 w for 12 w	Mesalamine, corticosteroids/AZA/6-Mp	54/24	Randomized, double blind	UC (UCDAI ≥ 4)	12 w: 43.3% with TSO vs 16.7% placebo (<i>P</i> = 0.04) [†]	No
Elliott et al ¹²⁰	<i>T. suis</i>	2500 TSO every 2 w for 12 w	Mesalamine, corticosteroids/AZA/6-Mp	?	Randomized, double-blind, crossover of Summers et al, 2005	UC (UCDAI ≥ 4)	12 w: 56.3% with TSO vs 13.3% placebo (<i>P</i> = 0.02) [†]	No
Kradin et al ¹²⁵	<i>T. suis</i>	5 × 1500 TSO	Refractory to corticosteroids, thalidomide, AZA, and α-TNF	1/0	Case report	CD	No benefits	Worms reached adult stage
Broadhurst et al ¹²¹	<i>T. trichiura</i>	3× eggs (500, 1000, 2000) in 3 y	Refractory to mesalamine 6-Mp and steroids.	1/0	Case report	Severe UC	Induction of remission	No severe adverse events
Sandborn et al ¹²³	<i>T. suis</i>	500, 2500, and 7500 TSO	5-ASA, prednisone, azathioprine, 6-Mp	27/9	Sequential dose-escalation randomized, double blind.	mild to moderate CD	na	Adverse events in 37% TSO vs 44% placebo patients; no dose dependency
Multiple sclerosis								
Benzel et al ⁴⁶ ; Rosche et al ⁴⁷	<i>T. suis</i>	TSO every 2 w over 6 mo	2/4 received methylprednisone	4/0	Nonrandomized, pilot study	Secondary progressive	Moderate immunomodulatory effect	1/4 mild gastrointestinal symptoms
Fleming et al ⁴⁸	<i>T. suis</i>	TSO every 2 w over 3 mo	2/5 previously received corticosteroids. Declined standard treatment.	5/0	Baseline vs treatment	Relapsing remitting, newly diagnosed	Reduction of new gadolinium-enhancing MRI lesions (n-Gd+).	3/5 mild transient gastrointestinal symptoms

(Continued)

Table IV. (Continued)

Citation	Nematode	Dose and dosage	Baseline medication allowed	n/Placebo	Kind of trial	Severity	Outcome	Adverse effects
Voldsgaard et al ⁴⁹	<i>T. suis</i>	TSO every 2 w over 3 mo	6/10 received IFN- β	10/0	Baseline vs treatment	Relapsing	No benefits	6/10 mild gastrointestinal symptoms
Allergic rhinitis Bager et al ^{46,37} , Bourke et al ³⁸	<i>T. suis</i>	8 $\times$ 2500 TSO every 21 d	No use of systemic steroids during the last 2 mo and no immune therapy in the last 2 y.	96/47	Double blind, placebo controlled	na	G	Gastrointestinal disorders (76% TSO vs 49% placebo). Moderate to severe flatulence, diarrhea, and upper abdominal pain, especially form d0-d42.

Abbreviations: 5-ASA, 5-aminosalicylic acid; AZA, Azathioprine; CD, Crohn disease; CDAL, Crohn disease activity index; IBD, inflammatory bowel disease; IFN, interferon; 6-Mp, 6-Mercaptopurine; TNF, tumor necrosis factor; TSO, *T. suis* ova; UCDAI, ulcerative colitis disease activity index; na, not assessed.
^aRemission defined according to the IBD quality-of-life index. Among the CD patients, 3/4 remitted and 4/4 responded (Δ CDAI $>$ 150). All the UC patients responded (SCCAI $>$ 4).
^bResponse defined as Δ UCDAI $>$ -4 point. Calculated according intention to treat.
^cResponse defined as Δ CDAI $>$ -100 points. Remission defined as CDAL $<$ 150.

gluten prevents histology and serology changes after gluten challenge.⁹⁰ The study enrolled 12 patients with diet-managed coeliac disease. Among them, 2 subjects withdrew after microchallenge with 1 g gluten. This promising study calls for a larger, double-blinded trial testing the efficacy and safety as well as the relative importance of *N. americanus* infection and gluten microchallenge.⁹⁰

H. PYLORI-INDUCED GASTRITIS

Helicobacter infections cause gastritis and peptic ulcer disease and predispose to metaplastic changes. In mouse, pretreatment with *H. polygyrus* limits the extent of *H. felis*-induced gastritis 16 weeks after infection.⁹¹ A similar protection is observed in coinfecting gerbils, where the gastritis indices appear inversely proportional to worm burden. However, the initial protective overexpression of anti-inflammatory mediators is only transient and is followed by a downregulation at week 42.⁹² Male insulin-gastrin transgenic mice suffer from a moderate chronic gastrinemia and develop gastric intraepithelial neoplasia 5–7 months after *H. pylori* infection. A recent study showed that male insulin gastrin mice preventively infected with *H. polygyrus* were less susceptible to *H. pylori*-induced gastritis and were resistant to gastric colonization with enteric microbiota, a phenomenon that is thought to contribute to gastric carcinogenesis in humans and mice.⁹³

INFLAMMATORY BOWEL DISEASES

In 1992, Elliot and Weinstock showed the first preliminary evidence that exposure to *H. polygyrus* reduces colitis in IL-10-deficient mice.⁹⁴ In mouse, *H. polygyrus* showed protective and therapeutic potential in chemically induced colitis, T-cell transfer colitis, and antigen-driven colitis. The polarization of DC by E/S products⁹⁵ might be a key factor in the observed induction of anticollitogenic IL-10-producing Treg.⁹⁶ However, the beneficial modulation of the immune response exerted by *H. polygyrus* dampens protective responses such as phagocyte recruitment. This leads to impaired resistance to a concomitant infectious colitis caused by pathogens such as *Citrobacter rodentium* and *Salmonella*.^{97,98}

The results with *H. diminuta* are less clear. Administration reduces the severity of a subsequent DNBS colitis in mice via the induction of aaMac, IL-10-producing T cells, and TGF- β -producing regulatory B cells.⁹⁹ In contrast, administration of *H. diminuta* larvae to dextran sodium sulfate (DSS) mice fails to improve the histologic damage, despite the induction of a Th2 polarization.¹⁰⁰ The enhanced Th2 response and eosinophilia are probably the reason for the detrimental effect of

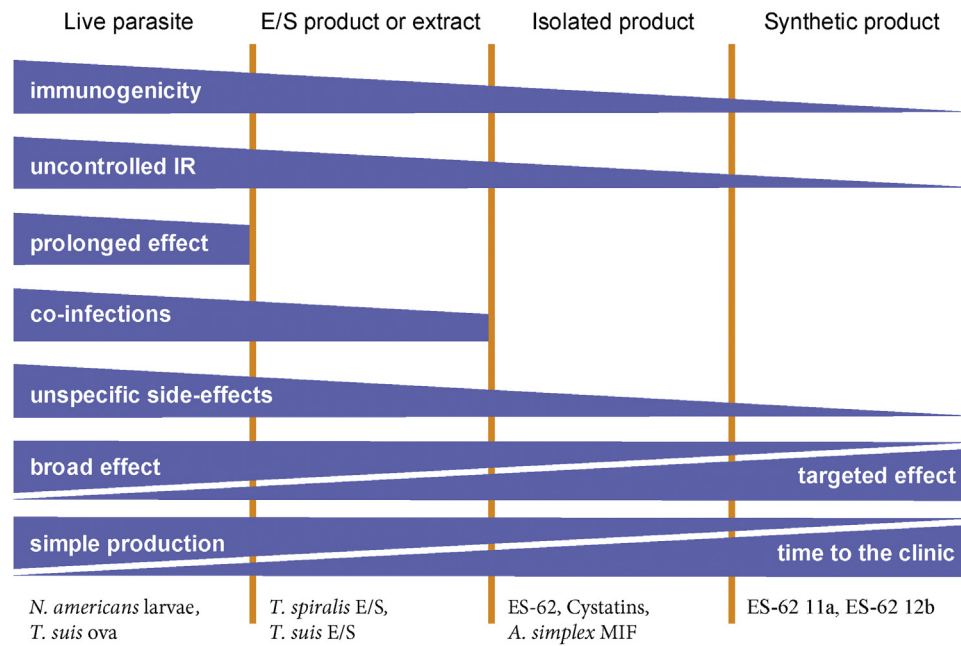


Fig 2. Helminth therapy can be applied by using either live parasites– or parasite-derived products. Extracts, lysates, or E/S can be further purified to identify and isolate selected components with improved characteristics. As an alternative, parasite molecules can be used as template to generate synthetic drugs. IR, immune response; E/S, excretory/secretory products; MIF, macrophage inhibitory factor.

H. diminuta observed in the Th2-biased model of oxazolone colitis.¹⁰¹ Mice injected with freeze-killed *S. mansoni* eggs 4 days before the induction of colitis show a STAT6-dependent attenuation of TNBS colitis, with an augmented Treg and Th2 response.¹⁰² Freeze-killed *S. japonicum* eggs also protect from TNBS colitis preventing the disruption of tight junctions and reducing the TNBS-induced TLR4 and NOD2 upregulation, leading to a Th2 polarization.¹⁰³ Similarly, *S. japonicum* soluble egg antigen protects mice from T-cell transfer colitis by reducing the Th1 and Th17 responses in favor of Th2 responses.¹⁰⁴ In contrast, as observed with *H. diminuta*, *S. japonicum* products are ineffective in acute DSS colitis despite inducing a Th2 shift.^{105,106} Furthermore, egg-laying *S. mansoni* infection—with male and female worms—increases the symptoms of DSS colitis. The noxious effect is ascribable to the eggs, as nonproductive infection with male larvae attenuates DSS colitis and diminishes both Th2 and Th1 cytokines levels. Another nematode, *T. spiralis*, induces a Th2 response that attenuates subsequent TNBS colitis.¹⁰⁷ As for other parasites, protection is reproducible using a *T. spiralis*-derived antigen,¹⁰⁸ with a downregulation of inducible nitric oxide synthase and IL-1 β and an upregulation of colonic Th2 and aaMac markers. In vitro experiments suggest an alternative activation of macrophages that in response to *T. spiralis* antigens upregulate arginase-1, mannose receptor, Ym1, and

IL-10 in a STAT6-dependent, IL-4R-independent manner.¹⁰⁹

T. muris is a natural mouse parasite. Hence, it is not surprising that concomitant infections worsen colitis in the IL-10^{-/-}, Mdr1a^{-/-}, and DSS model.¹¹⁰ Yet, when DSS colitis is induced after the expulsion of *T. muris* (from day 27 after infection), mice develop a milder colitis, and the regeneration of the colonic mucosa is faster.¹¹¹ Similarly, *T. trichiura* attenuates idiopathic chronic diarrhea in macaque monkey, inducing a Th2 response and changes in the microbiota composition.¹¹² The *A. simplex* MIF-II homologue tested in asthma model also reduces the severity of a subsequent DSS colitis. In vitro, *A. simplex* MIF-II induces expression of IL-10 by epithelial cells, DCs, and fibroblasts as well as TGF- β by fibroblasts.¹¹³ *A. vitae* cysteine protease inhibitor (cystatin) acts on macrophages and attenuates DSS colitis.²² Interestingly, *A. vitae* cystatin and cystatin from other helminthic parasites such as *Brugia Malayi*¹¹⁴ modulate cathepsin activities and antigen presentation by antigen-presenting cells, whereas the cystatin produced by the free-living *Caenorhabditis elegans* does not.²² To directly target the site of inflammation, *A. vitae* cystatin was cloned in the probiotic *E. coli* Nissle and administered to DSS-fed mice. Attenuation of colitis was associated with a decrease in macrophages, an increase of Treg in the colon, and a local decrease in the production of IL-6 and IL-17A.¹¹⁵

Table V. Helminth-derived molecules with immunomodulatory properties

Molecule	Class	Parasite	Model tested	Mechanism
rCKBP	Chemokine-binding protein	<i>S. mansoni</i>	Air pouch, CXCL8-airway inflammation	↓ Chemokines induced infiltration of neutrophils
CPI-2	Cystatin	<i>B. malayi</i>	—	↓ Endosomal/lysosomal proteases involved in antigen processing in a B-cell line ↓ MHC-II restricted antigen presentation
Cystatin	Cystatin	<i>A. cantonensis</i>	OVA-airway inflammation	↓ Eotaxin-1, eotaxin-3, MCP-1 (lung); ↓ Th2 CKs, IL-17A, OVA-specific IgE; ↑ IL-10 levels (serum)
Cystatin	Cystatin	<i>A. viteae</i>	OVA/grass pollen-airway inflammation	IL-10-producing Macs
Cystatin (cloned in <i>E. coli</i> Nissle)	Cystatin	<i>A. viteae</i>	DSS colitis	↓ IL-6 and IL-17A (locally) ↑ Treg, cathepsin inhibition: ↓ Ag presentation on APC
rCsStefin-1	Cystatin	<i>C. sinensis</i>	DSS colitis	↓ TNF- α in mLNs, ↑ IL-10 and IL-10 ⁺ F4/80 ⁺ Macs in spleen and mLNs
rOv17	Cystatin	<i>O. volvulus</i>	-	Cathepsin L/S inhibition: ↓ Ag presentation on APC, ↑ IL-10 by PBMC, ↓ HLA-DR, CD86 on monocyte
MIF-II	Cytokine	<i>A. simplex</i>	DSS colitis	IL-10 by IEC, DCs, and fibroblasts and TGF- β by fibroblasts
MIF-II	Cytokine	<i>A. simplex</i>	OVA-airway inflammation	IL-10 production and Tregs, IEC-TLR2 dependent
MIF-II	Cytokine	<i>T. trichiura</i>	—	↑ IL-10 and TNF- α from PBMC
Glycans	Glycan	<i>T. suis</i>	—	↓ LPS induced production of proinflammatory CKs (via CTL, MR) on DCs
LNFP III	Glycan	<i>S. japonicum</i>	EAE	↑ Th2 response
LNFP III	Glycan	<i>S. japonicum</i>	Flaky skin mice	Th2 priming DCs, via TLR4- NF- κ B axis
ω -1	Glycoprotein	<i>Schistosoma egg</i>	NOD mice	↑ FoxP3 IL-4
11a 12b	PC	<i>A. viteae</i>	OVA-induced airway inflammation	↓ Mast cell degranulation, CK production, Eos infiltration
PC moiety ES-62	PC	<i>A. viteae</i>	CIA	↓ IL-17/IL-22 in DC, γ/δ and CD4 ⁺ T (Th17) via MyD88 down-regulation (IL-1 R/TLR axis)
PC moiety of ES-62	PC	<i>A. viteae</i>	OVA-induced airway inflammation	↓ Th2 and Th17, ↑ Th1
rDiAg	Polyprotein	<i>Dirofilaria immitis</i>	NOD mice	↓ Anti-islet Th1 response, ↑ IgE by B cells, CD40 agonist, NO by Macs
rDiAg	Polyprotein	<i>D. immitis</i>	Murine spontaneous abortion	↓ IL-4, IL-23, and TNF- α
Mr85 Mr105	Porin	<i>T. muris</i>	—	ECM degradation (syncytial tunnel formation)
TsTCl	Serpin	<i>T. suis</i>	—	Inhibits Neutrophil elastase, the mast cell protease mMCP-1 and Cathepsin G.
rBmAsnRS	tRNA synthetase	<i>B. malayi</i>	T-cell transfer colitis	CD8 ⁺ response

Abbreviations: APC, antigen-presenting cells; CD, Crohn disease; CIA, collagen-induced arthritis; CK, cytokines; CPI-2, cysteine protease inhibitor-2; DC, dendritic cell; DSS, dextran sodium sulfate; ES, excretory/secretory antigen; IEC, intestinal epithelial cells; IgE, immunoglobulin E; IL, interleukin; LNFP III, lacto-N-fucopentaose III; LPS, lipopolysaccharide; Macs, Macrophages; MIF-II, macrophage inhibitory factor-II; mLN, mesenteric lymph nodes; MR, mannose receptor; NO, nitric oxide; NOD, nonobese diabetic; OVA, ovalbumin; PC, phosphorylcholine; rBmAsnRS, asparaginyl-tRNA synthetase; rCKBP, recombinant chemokine-binding protein; rDiAg, *D. immitis* recombinant antigen; rOv17, recombinant onchocystatin; TLR, toll-like receptor; TNF, tumor necrosis factor; Treg, regulatory T cells.

Besides cystatins, *B. malayi* also excretes an asparaginyl-tRNA synthetase that attenuates T-cell transfer colitis and induces a CD8⁺ response.¹¹⁶

CLINICAL STUDIES AND CASE REPORTS WITH TRICHURIS

The first small open-label trial with TSO was performed by the Weinstock group in 2003 with 4 CD and 3 ulcerative colitis (UC) patients (Table IV). The patients were treated with a single dose of 2500 TSO, and 6 of 7 patients achieved clinical remission at week 8. Yet, this effect was temporary, and 3 of the patients relapsed within 4 weeks. In 2 CD and 2 UC patients, the transient effect of TSO could be prolonged by repeated administration of TSO every 3 weeks for 28 weeks.¹¹⁷ A later open-label trial enrolled 29 CD patients, who received 2500 TSO every 3 weeks. At week 12, the symptoms improved in 22 patients and 19 entered remission.¹¹⁸ In a larger, double-blind trial with 54 UC patients, 13 of 30 patients receiving 2500 TSO every 2 weeks experienced a response after 12 weeks vs only 4/24 patients receiving placebo.¹¹⁹ After this first phase, in a crossover with patient that had not entered remission, 56.3% of the TSO patients responded (after 12 weeks) compared with 13.3% of the placebo patients. The number of patients included in this analysis is not clear, but the authors reported a significant effect.¹²⁰ In 2010, Broadhurst et al¹²¹ reported the case of a UC patient who improved its clinical symptoms by self-infecting with multiple doses of *T. trichiura* eggs. Along with the remission, a reduction in neutrophils infiltration and a mucosal regeneration characterized by the presence of CD4⁺ IL-22⁺ Th cells were observed. As summarized by Garg et al,¹²² the evidence in support of TSO for inflammatory bowel disease (IBD) remains inconclusive, and larger studies are required to reach a definitive conclusion and to separately assess the effects on UC and CD.

CONCERNS ON THE SAFETY OF TRICHURIS THERAPY

Although *T. suis* infections are presumably transient, self-limiting, and do not cause adverse effects in healthy subjects, their outcome in immunocompromised patients is not clear.¹²² The compromised epithelial barrier function in IBD patients might promote the invasion of the mucosa. Furthermore, the concomitant infection might enhance the inflammatory reaction as observed in *T. muris* infections of colitic mice.¹¹⁰ The initial studies performed in IBD patients did not report any adverse effect that could be attributed to the TSO treatment^{117,118} even in immunosuppressed patients.¹¹⁹ In a dose-escalation, double-blind test on CD patients, a similar rate of adverse effects was observed in both TSO and placebo groups, and no dose dependency

was noted.¹²³ These studies suggest that *T. suis* rarely reaches sexual maturity in the human host.¹²⁴ Yet, *T. suis* late-stage larvae were found in the cecal mucosa of a CD patient treated with TSO. In this case, treatment had no therapeutic efficacy, and the mucosa presented a eosinophils infiltrate even in sites not actively infected with *T. suis*.¹²⁵ The nature of IBD itself might mask the presence of TSO induced symptoms, thereby complicating the assessment of the TSO treatment-related effects. Supporting this concerns, MS and AR patients—receiving TSO developed gastrointestinal symptoms, although mild and transient even with concomitant immunosuppression.^{37,48,49,126} Finally, a productive infection with *T. suis* has been observed at approximately day 24 in 1 TSO-treated MS patient.¹²⁷

SUMMARY

The preventive potential of different helminths has been shown in different organic diseases models. Their therapeutic effect depends on the life cycle of the species and simultaneously targets multiple pathways. However, the therapeutic potential of each helminth is not clear, and different outcomes were observed depending on the helminth species and the animal model used. In contrast to the large spectrum of data derived from animal models (Table III), only few clinical trials in humans have been performed. Clinical trials with *T. suis* and *N. americanus* were performed in patients with allergy, multiple sclerosis, and IBD, but further evidence in larger studies is needed to prove or disprove their safety and efficacy (Table IV, Fig 2).¹²² The combined effect of a broad immunomodulation and human interindividual variability might further complicate the translation of a live parasite therapy to the clinic.

Moreover, FDA/EMA approval of a live biological agent may prove problematic. Methods of production, storage, and distribution are more challenging to develop for a live biological agent than those for a routine chemical medication. However, these problems have also been solved for new classes of drugs such as biologics.¹²⁸

Helminth E/S products have been tested in animal models as an alternative to live parasites (Table V).^{28,29} E/S products also are not completely risk free; they include a variety of poorly characterized components that might cause counterproductive effects or possess immunogenic potential. A safer approach might be the identification and isolation of selected products such as the LNFPIII and ES-62^{25,129} to reduce the extent of the side effects. Single components can be cloned into probiotic bacteria ensuring a targeted delivered (eg, into the intestine for intestinal diseases) and a prolonged release.¹¹⁵ Still,

many E/S products are large, potentially immunogenic molecules and appear unsuitable as a standard drug. To avoid this problem, they can be used as a basis for novel drugs with improved characteristic.^{26,27} This approach is surely promising; yet, the pipeline for the production of these analogue drugs is laborious and will not be readily available to the clinic.

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