Can helminths or helminth-derived products be used in humans to prevent or treat allergic diseases?

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Recent epidemiological and experimental data indicate that infection with helminths can protect humans from the development of allergic disorders by immunosuppressive mechanisms that involve the induction of IL-10 and/or regulatory T cells. Furthermore, helminth-derived immune modulators suppress allergic responses in mice. *Trichuris suis* therapy has been shown to be safe and efficacious in treating inflammatory bowel disease in humans. Has the time come to treat patients who have allergic diseases or healthy humans who are at risk of developing these diseases with helminths or helminth-derived products? Here, I discuss the pros and cons of such an approach.

Introduction

Allergic diseases are caused by allergen-specific responses initiated by CD4\(^+\) T helper 2 (Th2) cells. Th2 cells induce the development and recruitment of eosinophils, the contraction of airway smooth muscle cells, the production of mucus and allergen-specific IgE, which binds to Fc\(_{\text{e}}\) receptors on eosinophils, basophils and mast cells and mediates their degranulation by IgE cross-linking after contact with allergens. Although Th2 cell responses initiate and predominate during atopic disorders, Th1 and Th17 responses can also contribute to disease progression and severity, in particular in atopic dermatitis and atopic asthma [1,2].

In the past few decades, the incidence and severity of atopic disorders has steadily increased in developed countries and also more recently in developing countries (in particular in urban areas). The rise in both incidence and severity of atopic disorders has in the past been attributed, in part, to the steady decline of infectious diseases, a phenomenon called the ‘hygiene hypothesis’ [3]. This hypothesis suggests that exposure to infectious agents during early childhood prevents the development of allergen-specific Th2 cells because these agents establish Th1-based immunity [2,4,5]. However, recent epidemiological and experimental data indicate that other factors might contribute to, or be more important for, the observed increase in atopy [4–8]. These factors include increased pollution, widespread usage of antibiotics, exposure to endotoxin (particularly in a farming environment), lack of close contact with domestic animals, general change of diet and an altered gut flora [9]. Furthermore, the incidence of Th1-mediated autoimmune diseases has also increased steadily in recent decades, which suggests that the rise in allergic diseases cannot in general be explained by a lack of, or a reduction in, infections that induce Th1 responses [6,8].

What factor(s) is or was driving the increase in atopic disorders? There will certainly be more than one contributory factor and variation from patient to patient. Nevertheless, recent data clearly indicate that exposure to helminths could protect humans and animals from allergic disease. How can infection with helminths suppress the development or reduce the severity of atopic disorders? Although atopic Th2 responses and anti-helminthic Th2 responses are almost identical, there seem to be three identifiable differences. First, in contrast to an allergic response, infection with helminths often induce large amounts of polyclonal non-parasite-specific IgE. The second and third difference is that helminth infections usually do not cause allergic reactions and that during helmith infection (in contrast to allergic reactions) strong anti-inflammatory regulatory responses are also induced [7,10].

The protective effects of helminths on the development of allergic responses in animals have led to plans for the first clinical trial using helminths to treat allergic disorders or to prevent their development. The first allergic rhinitis trial is underway with an allergic asthma and celiac trials also initiated. Here, I discuss whether it is safe and effective to use helminths or helminth-derived products therapeutically to treat humans who have allergies or preventively to reduce the development of allergic responses in humans who are potentially at risk of developing them.

Do helminths protect from, enhance or exacerbate allergic responses?

The increase in allergic disorders in both developing and developed countries in most cases correlates with a decline in helmith infections. Because this trend is part of a generalized ‘westernization process’, it is not clear whether the lack of helmith infections is one of the reasons for the increase in allergic disorders or whether these two events are simply associated with the same general cause, for example better sanitation or different nutrition. However, recent epidemiological studies indicate that children infected with intestinal helminths (in particular, hook worms) or *Schistosoma* spp. have a reduced incidence of allergic responses [11–21]. Furthermore, patients who were treated with anti-helminthic drugs showed stronger...
atopic responses towards allergens after eradication of the helminths in some studies [21,22]. Taken together, these data clearly indicate that chronic infection with helminths might protect humans from allergic sensitization and responses. These findings are supported by numerous reports showing that infection of mice with *Strongyloides stercoralis*, *Heligmosomoides polygyrus*, *Nippostrongylus brasiliensis*, *Litomosoides sigmodontis* or male *Schistosoma mansoni* cercariae reduce allergic responses [23–31]. (For an extensive and concise review on this topic, please see Ref. [10].)

Nevertheless, some studies found no protective effects or enhanced allergic responses in helminth-infected patients (in particular *Ascaris* spp.), and anti-helminthic treatment of individuals living in regions with a high prevalence of worm infections resulted in an improvement in asthma [32–35]. Chronic helminth infections or exposure to helminth-derived products have also been linked to urticaria [36]. Severe allergic reactions after ingestion of fish contaminated with the nematode *Anisakis simplex* have been reported; however, this is a direct allergic response towards the helminth and not to a non-related allergen [6]. Animal experiments in which *N. brasiliensis*, *Brugia malayi*, *Toxocara canis* or *Trichinella spiralis* [37–40] were used also showed that helminths could induce or exacerbate allergic responses. Interestingly, infection with *N. brasiliensis* was linked to the breakdown of oral tolerance to the allergen [41]. Furthermore, aerosol challenge of cynomolgus monkeys that had been infected with *Ascaris suum* in the wild with *A. suum* antigen induces an asthmatic phenotype very similar to the human disease [42].

Taken together, it seems that some types of helminths favour the generation or exacerbation of allergic responses, whereas others seem to protect and some have controversial effects depending on the study. What is apparent is that there is no one clear picture, and the authors of a recent meta-analysis of all the published data came to the same conclusion [43]. Helminths that have an impact on the development of allergic disorders are listed in Table 1.

### Proposed immunological mechanisms by which helminths exacerbate, induce or suppress the development of allergic responses

Helminths almost exclusively induce strong Th2-type responses; therefore, they would be expected to promote atopy directly by the induction of IL-4, leading to increased development of allergen-specific Th2 cells (a study in mice supports this view [40]). Furthermore, the increase in total eosinophil numbers and induction of mastocytosis observed after worm infections might increase allergic-type inflammation directly. The mechanical irritation at sites of allergic inflammation during worm migration (for example in lung and gut) might also increase the atopic phenotype by usually increasing inflammatory responses at these sites and making allergens more accessible to uptake and presentation by antigen-presenting cells (APCs). Some helminths and helminth-derived products, for example *A. simplex*, might cause allergic symptoms directly by acting as an allergen [6].

Although there are some examples in which infection with helminths is associated with increased allergic responses, most studies suggest the opposite view [43]. For instance, it was found that the inverse association between the degree of infection with schistosomes and a positive skin-prick test was associated with the amount of IL-10 present in the serum of the patients [19]. This result led to the suggestion that IL-10 and/or transforming growth factor-β secreted by APCs or regulatory T (Treg) cells in response to a chronic helminth infection, directly interferes with allergic effector mechanisms by inhibiting mast cell degranulation or inhibiting Th2 cell proliferation [7,8]. This view is supported by studies showing that the suppression of allergic responses in mice infected with *N. brasiliensis*, *H. polygyrus* or *L. sigmodontis* was dependent upon or associated with the presence of IL-10 or CD4*"*Foxp3*"* Treg cells [6,7,10,24–31,44–46]. Nevertheless, there are other mechanisms by which helminths might also reduce allergic responses: (i) by the induction of alternatively activated macrophages, (ii) the IgE blocking hypothesis or (iii) by the induction of immunosuppressive B cells. Recent reports support the contention that helminth-induced alternatively activated macrophages might have a role in suppressing allergic disorders by directly suppressing T-cell effector functions [47,48]. The hypothesis that non-specific IgE induced by the helminth infection protects against mast cell or basophil degranulation by saturating the IgE binding sites on these cells, and thereby inhibits the binding of allergen specific IgE on these cells, is currently out of favour and there is little evidence to support it [49]. Furthermore, it was reported

### Table 1. Helminths reported to protect from, induce or exacerbate allergic responses

<table>
<thead>
<tr>
<th>Protection from Allergies</th>
<th>Refs</th>
<th>Inducing or exacerbating allergic responses</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiological studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Ascaris lumbricoides</em></td>
<td>[22]</td>
<td><em>Anisakis simplex</em></td>
<td>[6]</td>
</tr>
<tr>
<td>Intestinal helminths (in particular hook worm)</td>
<td>[11–16,23]</td>
<td><em>Ascaris spp.</em></td>
<td>[33,35]</td>
</tr>
<tr>
<td><em>Enterobius vermicularis</em></td>
<td>[12]</td>
<td><em>Fasciola hepatica</em></td>
<td>[36]</td>
</tr>
<tr>
<td><em>Schistosoma haematobium</em></td>
<td>[19,21]</td>
<td><em>Enterobius vermicularis</em></td>
<td>[20]</td>
</tr>
<tr>
<td><em>Schistosoma mansoni</em></td>
<td>[17,18]</td>
<td>Hook worm</td>
<td>[20]</td>
</tr>
<tr>
<td><em>Trichuris trichiura</em></td>
<td>[22]</td>
<td><em>Toxocara spp.</em></td>
<td>[34]</td>
</tr>
<tr>
<td><em>Oxyuris spp.</em></td>
<td>[16]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal experiments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Heligmosomoides polygyrus</em></td>
<td>[25–27]</td>
<td><em>Ascaris suum</em></td>
<td>[42]</td>
</tr>
<tr>
<td><em>Nippostrongylus brasiliensis</em></td>
<td>[28]</td>
<td><em>Brugia malayi</em></td>
<td>[38]</td>
</tr>
<tr>
<td><em>Litosomoides sigmodontis</em></td>
<td>[29]</td>
<td><em>Nippostrongylus brasiliensis</em></td>
<td>[37,41]</td>
</tr>
<tr>
<td><em>Schistosoma mansoni</em></td>
<td>[30]</td>
<td><em>Toxocara canis</em></td>
<td>[28]</td>
</tr>
<tr>
<td><em>Strongyloides stercoralis</em></td>
<td>[24]</td>
<td><em>Trichinella spiralis</em></td>
<td>[40]</td>
</tr>
<tr>
<td><em>Strongyloides venezuelensis</em></td>
<td>[6]</td>
<td><em>Schistosoma spp and Eggs</em></td>
<td>[10,30]</td>
</tr>
</tbody>
</table>

[76]
that *Schistosoma* infection induced regulatory IL-10-producing B cells that suppressed anaphylaxis and allergic lung inflammation [30,31]. It is also possible that the presentation of allergens by dendritic cells (DCs) that is needed for Th2 cell activation and development is influenced by the infection, resulting in a reduction in allergic responses. Taken together, the data from animal experiments indicate that IL-10 and/or Treg cells are responsible, at least in part, for the inhibition of allergic responses. However, although there is very limited evidence to suggest that this is also true in humans, a few papers support this view [50,51]. Figure 1 shows some potential mechanisms of how helminths might reduce allergic responses.

**Helminth-derived products that suppress or have the potential to suppress the development of allergic disorders in animals**

The results described earlier clearly show that some types of helminth suppress the development of allergic responses in animals and possibly in humans. Therefore, helminths could produce substances that directly interfere with the allergic response or with the development of allergen-specific Th2 responses. (For a detailed review on helminth-derived immune modulators, see Ref. [52].) This hypothesis is supported by reports that show that extracts from *A. suum* (ASC) suppressed the IgE antibody production against unrelated antigens and the generation of ovalbumin (OVA) peptide-specific Th2 responses in the airways [53]. The mechanism is not clear but might involve the production of IL-10 and the suppressive protein of *A. suum* (PAS-1) because the application of PAS-1 reduced the Th2 response and airway hyperreactivity (AHR) against the allergenic protein of *A. suum* (APAS-3) in the lung of mice [54]. This effect was associated with increased amounts of IL-10 observed in the bronchial lavage fluid of PAS-1-treated mice [54].

Another helminth produces substances that interfere with the generation of allergen-induced Th2 responses. We found that when *N. brasiliensis* excretory-secretory products (NES) were applied together with OVA in alum during the sensitization period, mice no longer developed allergen-specific Th2 responses, and the effect was independent of IL-10 [46]. Strong helminth-product-specific Th2 responses were induced in parallel with the inhibition of OVA-specific responses, which suggests that helminths suppress the development of an allergic response by secretin substances that modulate allergic responses without affecting the generation of helminth-specific Th2 immunity.

Cystatin also inhibits allergic responses in mice. Filarial cystatin, a secreted protease inhibitor, suppresses OVA-induced Th2 responses. This effect was dependent on macrophages and IL-10 but not on CD25+ Treg cells [47]. Interestingly, cystatin also reduced macrophage-mediated inflammation in a murine model of colitis induced by sodium dextran sulphate, which shows that the suppressive effects are not limited to allergic responses [47]. Again, the exact mechanism remains unknown.

The best characterized helminth-derived product shown to reduce allergic responses is probably ES-62, a molecule secreted by filarial nematodes (*Acanthocheilonema viteae*).
ES-62 directly inhibits the FcεRI-induced release of mediators from human mast cells by selectively blocking phospholipase-D-coupled, sphingosine-kinase-mediated calcium mobilization and nuclear factor-kappaB activation. ES-62 mediates these effects by forming a complex with Toll-like receptor 4. ES-62 also protects mice from allergic disorders and Figure 1 shows some potential mechanisms that could potentially affect the development of allergic disorders and Table 2 summarizes the helminth-derived products that could potentially affect the development of allergic disorders and Figure 1 shows some potential mechanisms of action.

**Table 2. Helminth derived products reported to protect from or have the potential to reduce allergic responses**

<table>
<thead>
<tr>
<th>Product</th>
<th>Derived from</th>
<th>Proposed mechanism of suppression</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult worm extracts from A. suum (ASC)</td>
<td>A. suum</td>
<td>IL-10</td>
<td>[53]</td>
</tr>
<tr>
<td>Cystatin</td>
<td>Acanthocheilonema vitae</td>
<td>IL-10</td>
<td>[47]</td>
</tr>
<tr>
<td><strong>Dirofilaria immitis-derived antigen (DiAg)</strong></td>
<td>Dirofilaria immitis</td>
<td>Unknown</td>
<td>[57]</td>
</tr>
<tr>
<td>ES-62</td>
<td>Acanthocheilonema vitae</td>
<td>Inhibits FcεRI mediated activation</td>
<td>[57]</td>
</tr>
<tr>
<td>Lyso-phosphatidylserine (lyso-PS)</td>
<td>Schistosoma mansoni</td>
<td>IL-10 and Th cells</td>
<td>[58]</td>
</tr>
<tr>
<td>Nippostrongylus brasiliensis excretory-secretory products (NES)</td>
<td>Nippostrongylus brasiliensis</td>
<td>Unknown</td>
<td>[46]</td>
</tr>
<tr>
<td>Ascaris suum</td>
<td>Fasciola hepatica</td>
<td>IL-10</td>
<td>[54]</td>
</tr>
<tr>
<td>Thioredoxin peroxidase</td>
<td></td>
<td>Alternatively activated macrophages</td>
<td>[59]</td>
</tr>
</tbody>
</table>

Some other helminth-derived products have the potential to reduce allergic responses, but they have not been tested yet in a model that is relevant to an allergic disease. These products include *Dirofilaria immitis*-derived antigen (DiAg) [57], schistosomal lysophosphatidylserine (lyso-PS) [58] and thioredoxin peroxidase produced by the trematode flatworm *Fasciola hepatica* [59].

These findings clearly indicate that helminths produce products that can, at least in animals, interfere with both the development of allergic responses and with effector mechanisms. Numerous groups are trying to identify novel products with similar properties, and more products will be identified, characterized and tested in vivo in the near future. Table 2 summarizes the helminth-derived products that could potentially affect the development of allergic disorders and Figure 1 shows some potential mechanisms of action.

**Which helminths or helminth-derived products have the greatest potential to treat or inhibit the development of allergies in humans?**

On the basis of the available epidemiological studies and animal experiments, several helminths might be considered for testing in humans. However, several points need to be considered. All evidence thus far points to the use of helminths (e.g. hook worms and schistosomes) that infect humans in developing but not in developed countries. Lack of infection with these parasites might explain the increase in allergies in developing but not in developed countries.

Which helminths are responsible for protecting humans living in developed countries from allergic disorders? The most common helminths infecting humans, in particular children, in developed countries are *Ascaris*, *Oxyuris* and *Enterobius*. The majority of data (humans, rodents and primates) indicates that *Ascaris* will exacerbate allergic responses but very little is known of the association of infections with *Oxyuris* or *Enterobius* infections and allergy, although one report suggests a protective effect of *Oxyuris* [16]. A further possibility is infections with different tape worm species or *Trichura* spp. No studies have addressed this issue so far and they would be hard to conduct because most of these parasites have been eradicated in humans in the developed world. A further point is that the strongest anti-inflammatory immune responses observed in humans are caused by long-lived helminths that cause chronic disease, for example *Schistosoma* spp., *Wuchereria bancrofti*, *Echinococcus* spp. or *Onchocerca volvulus*, and not by helminths that cause transient infections. Therefore, it would be expected that a chronic infection with a long-lived helminth, for which a strong anti-helminth Th2 response has the potential to cause massive tissue damage in the host (possibly a prerequisite for a strong anti-inflammatory response of the host), would offer the greatest therapeutic and preventive anti-allergy effects in humans. However, for obvious reasons, it is unlikely that clinical trials with one of these parasites will or should be conducted. By contrast, the hookworm *Necator americanus* was tested in dose-finding studies [60] and might be a suitable candidate. It is planned to test this approach in patients with asthma and other allergies [60]. Furthermore, studies using *Trichurus suis*, a whipworm that usually infects pigs and has been shown to be safe and effective in the treatment of inflammatory bowel disease (IBD) in humans [61,62], might also be considered. Supporting this view are reports showing that infections with helminths were able to suppress the development of some autoimmune diseases in animal models [63]. In this context it might also be important to note that a recent publication showed that infection with tapeworms exacerbated oxazolone induced colitis [64]. Nevertheless, in general, I believe that only parasites that reside within the GI tract will be used because of the expected non-severe side effects and the possibility of rapidly eliminating the parasites from the body by chemotherapy should the need arise.

A further interesting question is whether animal or human pathogens should be used. With animal pathogens, it is not clear whether some patients might develop an atypical infection and whether this particular helminth protects against atopy; with human pathogens, the effects are known and, at least for *N. americanus*, there is some evidence to suggest a protective role on atopy. Using known human parasites might eventually be a more effective and safer approach. This view is supported by a recent case report showing that a patient with IBD who was treated with *T. suis* surprisingly developed an iatrogenic infection in the gut [65], even though *T. suis* is considered to be a non-human pathogen. Furthermore, if children are treated, it is impossible to know whether a treatment with *T. suis* will have the same safety profile as in adults. Piglets are more susceptible to *T. suis* infection than adult pigs are [66].
A solution to these prospective problems would be to identify the products produced by the helminths that are causing the anti-allergic effects. Currently, there is most potential in testing ES-62 in humans to treat allergic disorders because its mode of action is at least in part known, and it interferes directly with an allergic effector function [55]. Other products also show some promise; however, little is known of the mechanism of action or off-target effects, and this could potentially hamper their development.

**Potential dangers of using helminths or helminth-derived products to treat allergies**

The side effects of using helminthic products in humans are unknown, and toxicological studies in animals including non-human primates are needed to answer this question. General immune suppression is always possible and might cause severe problems by increasing the risk of infections. The findings that some helminthic products also suppress responses other than Th2 responses [47,56] support this view. This is also true for helminth infections, which have been shown to suppress or reduce infection-induced Th1 responses, Th1-cell driven autoimmune responses and immune responses after vaccinations [6,10,23,45,67]. Using live helminths might also directly cause severe immune pathology and, in the case of helminths residing in GI tract, vomiting and diarrhoea, which are known to be associated with certain helminth infections. The advantage of using human pathogens is that the side effects are known, and anti-helminthic drugs (at least for most of the helminths) are readily available to kill the helminths when needed.

Further potential side effects of using helminths or helminth-derived products are anaphylactic or atopic reactions. Most helminth infections do not cause anaphylaxis in infected patients, even though many of the products produced by helminths can potentially cause anaphylaxis or allergic reactions. The most likely reason is that both the host and the parasite have developed mechanisms that inhibit anaphylaxis and allergic responses. For example, IgG4 specific for schistosome antigen inhibits IgE-mediated mast cell degranulation by the same antigen [68]. However, this is under natural conditions, and patients (in developing countries) are often infected at a very early age. It is possible that in some patients, with a special predisposition towards allergic diseases or already having allergies, allergic reactions towards the helminths or anaphylaxis might occur. It is also possible that helminth therapy will enhance allergic sensitisation and might exacerbate the development of an allergic disease in some of these patients. The same holds true for helminth-derived therapeutics, albeit to a lesser degree.

A further problem could be the crossreactivity of allergens with helminthic products. Patients treated with helminths might respond with an allergic response when they encounter a crossreactive allergen derived from pollen or another source. A recent report showing crossreactivity between tropomyosins from *A. lumbricoides* and cockroaches supports this scenario [69]. It also seems that, in general, helminth proteases are similar to known allergens [70].

**Implications for the clinical use of helminths to treat allergic disorders**

The current available treatment regimes for allergic disorders are efficacious and relatively safe, and have no severe side effects. Helminth or helminth-product-based therapy needs to be more efficacious and/or safer than the currently used standard anti-inflammatory therapies such as steroids, anti-histamines and specific immune therapy (SIT) (the latter is where increasing amounts of allergens are either applied sub-cutaneously or sub-lingually, resulting in allergen-specific Th1 and/or Tr responses counter-acting the allergen-specific Th2 responses). The costs of the novel therapy in comparison with the currently available drugs and therapies must also be considered because pharmaceutical companies (in most cases needed to shoulder the tremendous costs of the necessary Phase 2 and Phase 3 clinical trials) will only develop a novel therapy when it is potentially profitable.

For which type of allergy might helminths or helminth-derived products be tested? Because *T. suis* has shown a positive clinical outcome in IBD, it seems plausible that treating food allergies in the gut by helminths might be successful. However, the greatest medical need is for severe allergic disease, in particular asthma. Here, side effects can also be tolerated more readily. However, on the basis of current knowledge on atopic diseases and the limited success of SIT in these patients and other therapies [71], using helminths or helminthic products will not, in general, be able to cure or reduce allergic reactions in these patients. However, it is very likely that these patients will be the first to receive a helminthic-based therapy because they have the greatest medical need and hopefully some will benefit from this treatment. Treating mild to moderate atopic patients might be more successful, but potential side effects might not be tolerated because the therapy needs to be more efficacious than SIT and the currently used gold standards. This is highly unlikely.

The greatest opportunity could lie in treating children who are at risk (for example children from families in which both parents suffer from allergic diseases), before they develop an allergic disease. Potentially this could help to reduce the incidence of allergic diseases and stop the allergic march from rhinitis to asthma. However, treating healthy children with an experimental therapy raises many ethical concerns. Nevertheless, treating mild allergic patients or patients at risk with this type of therapy holds greatest promise because in both humans and animals established disease is always much harder to treat than it is to inhibit the development of allergic Th2 responses.

**Conclusions and implications**

It has long been known that helminths usually do not cause allergic reactions and can suppress immune responses. Only recently are we beginning to understand the underlying mechanisms (for example induction of Treg cells) and to identify products that might act directly as immune modulators. These observations have led to a discussion of whether helminths can be used to treat allergic patients. More research is needed before clinical trials, in particular in children, should be initiated, especially because the medical need (with the exception of very severe allergic...
diseases, for example steroid-resistant asthma) is not sufficient to warrant these novel approaches. Using helminths for these types of study might be premature. Although there is epidemiological data indicating that infections with helminths are associated with fewer allergic diseases, I am not convinced that this is a general phenomenon and that all patients will benefit from helminth infections because in all published studies a proportion of the infected patients still showed allergic responses. Furthermore, these studies have been conducted in developing countries, but the clinical trials will most likely be performed in developed countries with a high incidence of atopy. The authors of a recent meta-analysis of all the published data came to the conclusion that infection with nematodes usually do not protect against the development of allergic disorders [43]. A further point is that it is totally unclear what side effects can be expected, and in particular whether the ‘side effects’ are actually effects usually caused by the helminths. In a current dose-finding study using N. americanus, one volunteer (who received the highest dose of cercariae) had to be treated with mebendazole because of the infection, and most of the volunteers showed some type of adverse reaction [60]. The fact that four of the volunteers were authors of the study, and the authors write in the discussion that they believe ‘that on moral and ethical grounds we could not recruit volunteers to the study without being willing to undergo infection ourselves’ clearly suggests that the authors are aware that the treatment might not be entirely harmless.

On the basis of the success of a T. suis OVA therapy in IBD, it is conceivable to use the same therapy to treat allergic diseases. Again, I am not convinced that this approach will be efficacious for most allergic diseases with the possible exception of food allergies. T. suis therapy was shown to reduce IBD, which is mostly Th1 and/or Th17 response driven, and the site of inflammation is in close proximity to where the helminths are residing within the GI tract. The Th2 response possibly also generated by T. suis might also contribute to the protective effect (IL-4 is also a potent down modulator of macrophage activation, and Th2 cells also secrete IL-10.) If the protective effect is because of the induction of Treg cells in the GI tract, the close proximity might be necessary for the effect. Treg cells induced by T. suis might also have effects in other parts of the body (as shown in animal experiments for L. sigmodontis and H. polygyrus [26,27,29]) and suppress allergic responses in the skin and lung. However, because T. suis is not a human pathogen and does not cause any pathology, I cannot see why Treg cells (or other immune suppressive cells) should be activated in sufficient numbers to have an effect outside the GI tract because activation of Treg cells during infection usually requires a pro-inflammatory immune response, which is then dampened by the regulatory response induced by both the parasite and the host [67]. However, T. suis might harbour immune modulators that selectively activate Treg cells without causing any or only mild pathology.

In conclusion, there are still more questions than answers in respect to helminth-mediated protection of allergic disorders. Is a helminth-based therapy really safe in all patients? How often and how long must the therapy be performed to be efficacious? What is the mechanism of protection? Furthermore, epidemiological data are inconclusive, and although many but not all animal experiments, including our own, clearly show that infections with helminths can reduce allergic responses, it is important to keep in mind that these data have been generated in more or less immunologically naive mice, not in therapeutic settings, and with helminths that are not suitable for human use. I am not convinced that these results will be predictive for therapies tested in humans. Furthermore, on the basis of the complexity of both atopic diseases and anti-helminth immune responses, and the complex biology of helminths, it is very likely that this approach might ultimately fail because one or a few products from helminths might not have sufficient therapeutic effects. However, applying safe and effective products repeatedly might overcome this potential problem, and using them as an adjuvant together with allergen could also be an option. Furthermore, using helminths might be efficient only when large amounts are used. This, in turn, might cause unacceptable side effects for diseases that are not life threatening and are currently more or less well controlled by steroids and other medications. Nevertheless, I would be very happy to be proven wrong and for a novel, effective and safe therapy for allergic disorders either using helminths or helminth derived products to become available in the future. Extensive testing of these types of approaches first in diseases with an unmet medical need (for example multiple sclerosis, rheumatoid arthritis or severe IBD), might pave the way for a safe therapy in atopic patients.

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Opinion

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