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Review article

Geohelminth infections: a review of the role of IgE and assessment of potential risks of anti-IgE treatment

Geohelminth infections are major parasitic infections with a worldwide distribution. Immunoglobulin E (IgE) is considered to play a central role in protective immunity against these parasites although the evidence from experimental animal models infected with helminth parasites and treated with anti-IgE antibodies and from observational studies in human populations of the immunologic correlates of protective immunity against helminths do not support a critical role for IgE in mediating protection against helminths. Anti-IgE treatment of human allergic disorders using a humanized monoclonal IgE antibody (omalizumab, Xolair) has been approved for clinical use in the USA and Europe and there is concern that this treatment may be associated with increased morbidity in populations exposed to helminth infections. A recently published randomized controlled trial investigating the risk of geohelminth infections in allergic patients receiving omalizumab in Brazil has provided some evidence that omalizumab may not be associated with increased morbidity attributable to these parasites. This review examines the evidence for a role of IgE in protective immunity against helminth parasites, discusses the findings of the randomized controlled trial, assesses the potential risks and provides recommendations for anti-IgE treatment in groups of allergic patients with different exposure risks for helminth infections.

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Helminth parasites are highly prevalent worldwide and they particularly affect poor populations living in underdeveloped regions of the Tropics. Geohelminth (intestinal helminth) infections are the most prevalent of the helminth parasites and include *Ascaris lumbricoides*, *Trichuris trichiura*, hookworm and *Strongyloides stercoralis*. Other important helminth infections include those caused by schistosome and filarial parasites.

Helminth allergens are potent inducers of immunoglobulin E (IgE) production and stimulate strong IgE responses in humans (1). Immunity to helminth parasites is characterized by the production of type-2 cytokines (i.e. IL-4, IL-5 and IL-13) that induce multiple effector pathways including those mediated by IgE. The actual importance of IgE in protective immunity against helminth parasites is not clear, but may contribute to host immunity against specific helminth parasites or life-cycle stages.

A humanized monoclonal anti-IgE antibody approved in the USA for treatment of patients with moderate-to-severe allergic asthma and in the European Union (EU) for severe allergic asthma (omalizumab, Xolair®; Genentech Inc., South San Francisco, CA, USA) binds to serum free-IgE and prevents IgE from interacting with mast cells and other effector cells. Because of the presumed role of IgE in helminth infections, it is theoretically possible that omalizumab could increase susceptibility to helminth infection and be associated with increased clinical morbidity caused by these parasites. Omalizumab is now available for the treatment of asthma in many countries where helminth infections are more prevalent or endemic and there is concern about potential morbidity occurring among individuals who receive omalizumab treatment and who are exposed to helminth infections.

Epidemiology of geohelminth infections

Geohelminth parasites can infect humans in almost all geographic and climatic regions except for those where extremes of cold or heat make survival of infectious stages impossible. Prevalences are highest in warm, moist climates in Tropical and Subtropical regions and are

strongly associated with poverty, poor environmental hygiene and neglected health services. The estimated global prevalences of *A. lumbricoides*, *T. trichiura*, hookworm and *S. stercoralis* infection are 1.5 billion, 1.3 billion, 900 millions and 70 millions respectively (2).

Other important helminth infections include schistosomiasis (200 millions infected) and filariasis (140 millions). Although schistosomiasis and filarial infections have worldwide distributions, in the Tropics, these infections tend to have a focal distribution within endemic countries restricted by the presence of an infection reservoir and intermediate hosts or anthropophilic vector species.

Morbidity caused by infections with ascariasis, trichuriasis and hookworm is strongly associated with infection intensity (3) and tends to be restricted to heavily infected children and vulnerable adults (e.g. women of childbearing age) with significant and prolonged exposure histories. *Strongyloides stercoralis* infection can occasionally cause a potentially fatal condition, the hyperinfection syndrome, when the human host is immunocompromised allowing the unrestricted replication of *Strongyloides* larvae outside the intestine. However, the vast majority of helminth infections do not cause clinical disease. The WHO estimates that in those areas where such infections are a public health concern (e.g. endemic areas in the Tropics), the prevalence of associated disability is low compared with the overall infection rates (Table 1). Helminths are unable to replicate within the human host (except *S. stercoralis*) and therefore the rates of clinical morbidity presented are relevant only to endemic communities where the opportunities for repeated and prolonged exposure allow significant worm burdens to become established. Morbidity associated with short-term exposure (e.g. temporary travellers to endemic areas) and very small parasite burdens is likely to be considerably less.

Role of IgE in protective immunity against helminth parasites

The mechanisms of protective immunity against helminth parasites are not well understood but generally are considered to be associated with Th2 immune responses (4). The important host protective mechanisms are likely to vary between different helminth parasites and different life-cycle stages of the same parasite that may inhabit different host tissues.

Important protective mechanisms against geohelminth parasites include: altered intestinal physiology, such as changes in intestinal mobility and mucus production creating an environment hostile to intestinal helminths (5); mucosal mastocytosis and eosinophilia that may be important in mediating expulsion against some helminth parasite stages – IgE-mediated activation of mast cells leads to rapid expulsion of adult forms of some helminths (e.g. *Trichinella spiralis*) (6); mast cell activation and recruitment of immune effector cells, such as Th2 cells, eosinophils and macrophages that localize the host immune response; and immune reactions directed against invasive larvae (e.g. schistosome schistosomula and geohelminth and filarial larvae) are accompanied by local tissue eosinophilia and killing or immobilization of helminth larvae within eosinophil-rich inflammatory infiltrates. Immunoglobulin E, therefore, may contribute to protective mechanisms by activating host immunity. People living in endemic areas for helminth infections tend to have very high levels of polyclonal IgE on account of chronic helminth exposure. Helminth parasites are potent polyclonal inducers of IgE. It has been suggested that high levels of polyclonal IgE are a helminth defense mechanism against the effects of anti-parasite IgE (7). Nonspecific IgE may saturate FcεRI receptors on basophils and mast cells and prevent antigen triggering of mast cell degranulation (8). Likewise, saturation of FcεRII (low affinity) receptors with nonspecific IgE on antigen presenting cells may prevent optimal IgE-dependent presentation to T cells (9). However, studies of human helminth infection sera from highly parasitized populations show that IgE levels are rarely high enough to interfere with basophil activation by cross-linking of allergen-specific IgE (10).

Role of IgE in protective immunity against specific parasites

Ascariasis

Children living in endemic communities that appear to be resistant to infection with ascariasis have higher levels of

Table 1. WHO estimates of numbers infected and at risk of disability for *Ascaris, Trichuris* and hookworm infections for 6 World Bank Regions (EU not included)

Parasite	Population (millions)	Infections (millions)	Infections (%)	Population at risk of disability (millions)	Population at risk of disability (%)	% of infections with disability
Ascaris lumbricoides	4120	1382	33.5	14.8–62.3	0.3–1.5	1.1–4.5
Trichuris Trichuria	4120	1007	24.4	18.4–45.5	0.5–1.1	1.8–4.5
Hookworm	4120	1250	30.34	36–151	0.9–3.7	2.9–12.1

World Bank Regions include: Sub-Saharan Africa, India, China, Other Asia & Islands, Latin America & Caribbean, Middle Eastern Crescent.
WHO, Intestinal Nematode infections, Report on Global Epidemiology of infections diseases (53).
Two estimates of risk are presented whereby the lower threshold corresponds to a higher potential disability. These represent empirical observations of the developmental and clinical symptoms associated with burdens of the individual worms [ascariasis uses deficits in growth and fitness; trichuriasis uses growth stunting (low) and colitis (high); hookworm uses anemia].

IgE against the major *Ascaris* allergen, ABA-1, than do heavily infected children (11), and the presence of anti-ABA-1 IgE is a correlate of immunity with increasing age after 12 years (12). There is a probable role of type-2 cytokines in mediating protective immunity, with increasing levels being associated with an age-dependent reduction in infection intensity (13). Additionally, increased susceptibility to reinfection is associated with weak type-2 responses (IL-5 and IL-13) (14). Taken together, the evidence indicates that type-2-mediated effector mechanisms may be important in mediating protective immunity in chronically infected children that may or may not involve IgE.

Trichuriasis

Cross-sectional immunoepidemiological studies of human *T. trichiura* infections have provided some evidence for a protective association with parasite-specific IgA (15) and IgE (16). A more recent study has provided evidence for a role of type 2 cytokines in mediating protective immunity against trichuriasis in children (14).

Hookworm

Negative associations have been observed between hookworm parasite burden and parasite-specific IgG, IgM and IgE antibody levels (17–19). Children living in endemic areas of Brazil and who appear to be resistant to hookworm infection produce greater levels of both type-1 (IFN-γ) and type-2 cytokines compared with chronically infected children (20), and a treatment study of infected adults from a highly endemic area of Papua New Guinea provided evidence that resistance to reinfection following treatment was associated with the type-2 cytokine, IL-5 (21). Together these data indicate a potential role for both type-1 and type-2 cytokine-mediated mechanisms in protective immunity.

Strongyloidiasis

Individuals with suppressed immunity [because of immunosuppressive treatments, such as oral or intravenous steroids, malignancies or Human T cell lymphotropic virus-1 (HTLV-1) co-infection] are at risk of uncontrolled parasite replication that may cause the hyperinfection syndrome. Individuals co-infected with HTLV-1 and *S. stercoralis* appear to have a reduced capacity to control larval replication (22–24) and have deficits in parasite-specific IgE (22, 24–27). An increased prevalence of both *S. stercoralis* and *Schistosoma mansoni* infections have been described recently among individuals infected with HTLV-1 (28) suggesting that common mechanisms, specifically a generalized suppression of type 2 immunity may mediate increased susceptibility to these infections (29).

Schistosomiasis

People who appear to be resistant to infection with schistosomiasis despite being exposed to infection have enhanced type-1 cytokine responses (30). There is evidence for a protective role for IgE during chronic human schistosome infection, but none are direct and all are correlational. Most of this evidence is derived from immune correlates of resistance to reinfection after treatment. Several studies have provided evidence for an association between parasite-specific IgE (31, 32) and type-2 cytokines (33) and resistance to reinfection. Protective immunity to schistosomiasis infection is likely to be mediated through multiple effector pathways that are associated with a type-2 cytokine phenotype, and IgE may be one of many overlapping immune components that participate.

The effects of anti-IgE treatment on helminth infections

Effect of anti-IgE treatment in animal models of helminth infections

The impact of anti-IgE antibodies on parasite burdens has been examined in animal models of *S. mansoni*, the lung fluke *Paragonimus wetermani*, the filarial nematode *Onchocerca volvulus* and *Strongyloides ratti* infections. Following anti-IgE treatment, despite undetectable levels of IgE, there was a reduced parasite burden in mice infected with *P. westermani* (34), and decreases in the number of adult worms and the number of eggs produced per worm in mice infected with *S. mansoni* (35). The protective effect of anti-IgE in these models may be on account of suppression of nonspecific IgE levels leading to more parasite-specific and focused immune response (34) or enhanced IgE-dependent cellular cytotoxicity to parasitic worms mediated by superior binding of parasite-attached IgE to FcεRII/CD23 on macrophages and eosinophils. Parasite burdens during experimental infections with *S. ratti* were, however, not affected by anti-IgE treatment (36), and there was some evidence for an increase in survival of L3 stage *O. volvulus* larvae after treatment with anti-IgE (37).

Effects of anti-IgE in human populations exposed to helminth infection

Considering the potential role for IgE in the human immune response against helminth parasites, the safety of anti-IgE and the risk of infection with geohelminths were investigated in an exploratory randomized controlled trial (38).

This randomized, 52-week, double-blind, placebo-controlled study evaluated the effect of subcutaneous omalizumab treatment (every 2–4 weeks) on parasite infection in 137 Brazilian patients (aged 12–30 years) with allergic asthma and/or perennial allergic rhinitis and who

were considered to be at high risk of geohelminth infection. All patients received adequate anthelmintic treatment before the start of the study to achieve 'parasite-free' status. During the study, patients were assessed at monthly intervals and anthelmintic treatment was provided whenever parasites were detected above predefined infection intensity thresholds.

Anti-IgE treatment did not appear to be associated with increased morbidity attributable to geohelminths as assessed by clinical and laboratory monitoring. However, during the 52-week treatment period, slightly more omalizumab-treated subjects [50%, (34/68)] experienced one or more geohelminth infections compared with placebo-treated subjects [41% (28/69); OR 1.47, 95% CI: 0.74–2.95, one-sided $P = 0.14$; Table 2], providing some evidence for a potential increased incidence of geohelminth infection in subjects receiving anti-IgE therapy, but the possible excess infection risk was considered not to be clinically significant and overall clinical outcomes were unaffected. The study also assessed safety using several parasitological parameters designed to detect rapid acquisition of new infections (time to first infection), the rapid acquisition of heavy helminth parasite burdens (time to treatment with anthelmintics), and a tendency for higher helminth infection intensities (maximal infection intensity and requirement for additional anthelmintic treatments). These parameters did not appear to be affected by anti-IgE therapy. Overall, the study findings indicated a potential increased risk of re-infection with common geohelminth parasites (specifically *A. lumbricoides* and *T. trichiura*, Table 2) following omalizumab therapy in a population considered to be at high risk of infection, but the potential increased risk did not appear to be associated with increased morbidity.

Limitations of this exploratory study were the relatively small sample size and the low power to detect a small increase in the risk of geohelminth infection. The study may also have been subject to a selection bias – there were major difficulties in identifying allergic subjects who were at high risk of infection and had levels of total IgE ≤ 1300 IU/ml, an inclusion criterion for the trial. Additionally, allergic patients appear to have a low risk of infection with geohelminth parasites [reviewed in Cooper et al. 2006 (39)]. As a result, the allergic patients studied were at very much higher risk of infection than might be expected in the EU or the USA populations that receive omalizumab, but possibly at lower risk of infection than the nonallergic population living in the study areas.

The study also assessed the parasitological response to anthelmintic treatment. There did not appear to be differences in cure rates for geohelminth parasites between treatment groups. Treatment with omalizumab is unlikely to affect the efficacy of treatment for adult geohelminth parasites in the intestinal lumen but could potentially reduce the efficacy of anthelmintic treatments for intravascular or invasive larvae. In the latter cases, the efficacy of anthelmintic drugs may be partially dependent on immune mechanisms that could involve IgE. For example, the efficacy of ivermectin against strongyloidiasis among individuals with immune defects (i.e. HTLV-1) appears to be reduced (40), but it is unknown how this relates to either global immune deficits or specific deficits of IgE observed in co-infected patients.

There were too few infections with *Strongyloides* to allow an evaluation of safety in this study. Some concern for a potential increased risk of *Strongyloides* hyperinfection in subjects taking omalizumab is justified, although the risk may be less than with other more broadly immunosuppressive treatments such as oral steroids that have been associated with hyperinfection (41). Hyperinfection has been associated with a high

Table 2. Number of infections reported by patients with geohelminth parasites during the treatment period (intent-to-treat patients) (38)

	Omalizumab ($n = 68$)		Placebo ($n = 69$)	
	Total number of patients with infection, *n* (%)	Total number of infections	Total number of patients with infection, *n* (%)	Total number of infections
Geohelminth infection*	34 (50.0)	60	28 (40.6)	42
Ascaris lumbricoides	21 (30.9)	28	16 (23.2)	16
Hookworm†	5 (7.4)	5	8 (11.6)	8
Trichuris trichiura	15 (22.1)	15	9 (13.0)	10
Enterobius vermicularis	11 (16.2)	12	6 (8.7)	6
Strongyloides stercoralis	0	0	2 (2.9)	2
Other helminth infections	4 (5.9)	4	3 (4.3)	3
Hymenolepis nana	0	0	2 (2.9)	2
Schistosoma mansoni	4 (5.9)	4	1 (1.4)	1
Enteric protozoa infections‡	34 (50.0)	47	31 (44.9)	43

*$P = 0.06$ for overall comparison of geohelminth infection rate (repeated measures logistic regression with treatment, dosing schedule, centre and study visit as factors. †*Ancylostoma* and *Necator* spp. ‡Protozoa identified were *Blastocystis hominis, Chilomastix mesnili, Endolimax nana, Entamoeba coli, Entamoeba histolytica, Giardia intestinalis and Iodamoeba butschlii.*

mortality (up to 86%) (42) and involves the conversion of rhabditiform to filariform (infectious) larvae within the intestinal tract. The filariform larvae can enter the vascular system and invade any organ, leading to severe complications, such as sepsis, meningitis, peritonitis and endocarditis. Interestingly, hyperinfection has not been associated with acquired immuno-deficiency syndrome (AIDS) (42, 43).

Comparing the rates of helminth infection events in this study with that in the overall omalizumab clinical trial population, the data on the clinical course of infection represents a large number of events (equivalent to >60 000 patient-years exposure in a non high-risk population). In the omalizumab clinical trials programme, adverse event data were monitored and collected with only 1 (0.03%) reported helminth infection (*Enterobius vermicularis* or pinworm) from 1934 patient-years of omalizumab treatment in 3678 treated patients (one further patient reported an unspecified parasite infection). The parasite infection rate was similar in the control group where one case of *E. vermicularis* infection was reported in 1364 patients-years studied in 2452 patients. Further data are available from the USA with no spontaneous postmarketing reports of helminth infection received in over 50 000 patients treated in the moderate-to-severe asthma population eligible for omalizumab treatment. On account of the rare nature of the events, they will be continued to be monitored as more patients are treated over longer periods of time.

Epidemiological risks of infections with helminth parasites among individuals with asthma

An assessment of the potential risks of helminth infection in allergic individuals is a potentially important issue for physicians considering anti-IgE treatment for their patients. Several different helminth exposure risk groups require consideration: patients resident in nonendemic areas with no travel history to endemic areas; individuals resident within nonendemic areas but with a history of travel to or who are considering travel to endemic countries or are resident for significant periods in endemic countries; and individuals resident in endemic countries or those that migrate to nonendemic from endemic regions. Because of the paucity of data of infection risks with specific helminth parasites among patients receiving anti-IgE treatment, the following discussion considers helminth parasites in general but refers to specific parasites where relevant.

Individuals resident in nonendemic areas

Data on the epidemiology of helminth infections in individuals resident in the EU and the USA is limited, reflecting the fact that helminths are rare infections in these areas. Within the EU, geographical location is an important determinant of exposure risk; being extremely low for indigenous populations in northern Europe, but greater along the Mediterranean coastline where warmer and more humid conditions are more permissive for survival of the infectious life-cycle stages of geohelminth parasites (44–47). Economic status also appears to influence risk of geohelminth infection with poorer regions of eastern Europe at greater risk for ascariasis, hookworm and strongyloidiasis.

Individuals resident in nonendemic areas who travel to endemic areas, or are temporary- or long-term residents in endemic areas

The prevalence of helminth infection among travellers and expatriates returning to the EU or North America is low (Table 3). The risk of infection with soil transmitted parasites (*Ascaris, Trichuris,* hookworms) is likely to be extremely small among tourists who stay for short periods in relatively clean environments while travelling in endemic countries. The reported risk of strongyloidiasis among travellers appears to be extremely low, with

Table 3. Helminth infection prevalence data among travellers and expatriates

Parasite (or symptom of parasitic infection)	Whitty et al.*, 2000 (1990–1991) (50)	Whitty et al.*, 2000 (1997–1998) (50)	Brouwer et al.†, 1999 (1987–1995, *n* = 253) (54)	Schulte et al., 2002 (1995–1999, *n* = 14 298) (55)	Libman et al.‡, 1993 (1981–1987, *n* = 1605) (56)
Geohelminths (any) (%)	33/995 (3)	14/510 (3)	6.7	44 (0.3)	NS
Ascaris (%)	NS	NS	2	7 (0.05)	2.3
Trichuris (%)	NS	NS	3	4 (0.03)	2.4
Hookworm (%)	NS	NS	2	18 (0.1)	0.6
Strongyloides (%)	NS	NS	0.4	15 (0.1)	0.1
Giardia (%)	39/995 (4)	11/510 (2)	23	11 (0.08)	NS
Amoeba (%)	115/995 (12)	20/510 (4)	1	26 (0.2)	NS
Eosinophilia (%)	67/852 (8)	61/508 (12)	10	4.8	10.4
Schistosome serology (%)	72/676 (11)	83/483 (17)	8	41 (0.3)	1.3

NS, not specified. Numbers in parentheses alone are %.

*Patients referred for routine screening including symptomatic individuals (length of stay varied from 3 months to 45 years and included British government employees, employees of NGOs and VSO volunteers).

†Asymptomatic children returning home after living in the Tropics with stays extending from 3 months to 13 years.

‡Data from individuals attending a Tropical Disease Clinic after returning from the Tropics.

only 165 reported cases of strongyloidiasis among travellers between 1990 and 2003 in England and Wales (48), the majority being acquired in sub-Saharan Africa and the Indian sub-continent. The risks of schistosomiasis appear to be negligible for those who avoid contact with fresh water, although the number of cases among travellers returning to the UK may be increasing (49, 50), possibly reflecting different patterns of travel and travel pursuits (e.g. water sports in freshwater lakes).

Visitors to endemic areas that are exposed to helminth infections have generally low-level exposures and the infections that develop tend to be asymptomatic. Some infected visitors, particularly those with previous sensitization to helminth infections, may develop allergic-type reactions, such as asthma-like symptoms and localized dermatitis, urticaria and angioedematous swellings (51, 52). These reactions tend to be self-limiting and generally resolve without specific anthelmintic treatment. There are unusual circumstances in which infection may develop in individuals after starting anti-IgE therapy. For example, 'expatriate' workers from a nonendemic country already taking anti-IgE therapy for allergic disease may migrate to an endemic area and adopt a high exposure-risk lifestyle [e.g. volunteers in the US Peace Corps or UK Voluntary Service Overseas (VSO)]. Other high-risk groups include individuals with existing or newly-acquired *Strongyloides* infections that could belong to any of the infection risk categories.

Individuals resident permanently in endemic areas and residents of endemic areas who migrate to nonendemic areas

Long-term risks for residents of endemic areas involve potential morbidity associated with helminth parasite burden. Generally, most individuals in this category who will be considered for anti-IgE therapy will have low risks because of the apparent inverse relationship observed between allergy and chronic helminth infection (39). Socioeconomic factors may also lower the risk, for example, families with access to sanitation and clean water are generally at low risk of acquiring geohelminth infections. However, the risks should be considered on a country by country basis as public healthcare provision varies and therefore the likelihood of at-risk populations receiving omalizumab will similarly vary. Countries with better healthcare coverage for at-risk populations and where omalizumab is available may perceive a higher risk.

In some circumstances, populations in endemic countries that are at high risk of helminth infection may be considered for anti-IgE treatment if there are medical programmes in place that can support the high cost of these treatments. In such cases, individuals who are infected with helminth parasites and who remain continuously exposed to infection are likely to be ineligible for anti-IgE treatment because of high levels of total IgE (>700 IU/ml).

The likelihood of helminth infections in populations that migrate from endemic to nonendemic countries will depend on the countries and regions of origin as these affect both levels of exposure and the helminth parasites to which patients have been exposed. The rare helminth infections in these categories will tend to be of low infection intensity and unlikely to cause significant morbidity. Individuals with existing high parasite burdens, even if asymptomatic, are unlikely to have IgE levels within the omalizumab dosing schedule (i.e. <700 IU/ml) and therefore would not be eligible for this therapy.

Assessment of the usefulness of screening for helminth infections prior to starting omalizumab therapy

A summary of the assessment of risk for helminth infection in groups of individuals with different helminth exposures and the actions to be taken by physicians before prescribing omalizumab is provided in Table 4. The risk of helminth infection is negligible for patients with asthma in the EU and the USA and is very low for individuals with short-term exposure histories in endemic areas (i.e. through tourism) (Table 4). Clinical trial data and experience from the clinical use of omalizumab suggest that parasite infections are very infrequent in asthmatics treated with this therapy and that screening for helminth infections in patients with negligible to very low risks (Table 4) is not warranted.

The risks of infection are, relatively higher for migrants from endemic areas or residents of nonendemic areas that spend significant periods in endemic countries. It is not clear whether screening for helminth infections should be undertaken for these patients groups because the potential infection risks will vary widely. If the exposure

Table 4. Risk assessment of helminth infection and potential physician actions in populations receiving omalizumab treatment

Population group and helminth exposure level	General risk of helminth infection and morbidity	Physician action
USA and EU asthma population, minimal exposure	Negligible	None necessary
Short-term exposure (e.g. holiday travel)	Very low	None necessary
Prolonged exposure (e.g. Peace Corps, VSO)	Low	Screening for helminth infections should be considered
Migrants from endemic areas	Very low-to-moderate	if there is perceived to be a significant risk (see text)
History of strongyloidiasis (with ongoing exposure)	Hyperinfection syndrome	Consider screening for *Strongyloides* before treatment
or high risk of *de novo* infection	very rarely presents	

period has finished then screening is probably not warranted unless the individual has a past history of filarial and schistosome infections. In the latter case, an adequate and documented course of chemotherapy that has been shown to result in cure by follow-up investigations probably precludes the need for further assessment. However, current treatments for some filarial parasites are not curative (e.g. *O. volvulus*) or are sub-optimal (e.g. lymphatic filariasis) and further investigations to exclude the presence of these parasites may be necessary. If potential exposures to helminths are still present (e.g. continued residence in an endemic area), then screening for helminth infection is advisable. Periodic screening for parasites is routine for some of these groups (i.e. VSO and Peace Corps) and access to such laboratory records should be sufficient to assess potential risks.

Patients with a history of *Strongyloides* infection (and continuing exposure by residence in an endemic area) may warrant screening for this parasite on account of the possible risk of hyperinfection. Because *Strongyloides* is geographically ubiquitous in temperate, tropical and subtropical climates, recommendations for routine screening prior to omalizumab therapy should be restricted to individuals considered to be at greatest risk.

Assessment of the usefulness of screening for helminth infections whilst receiving long-term omalizumab therapy

Omalizumab is an asthma 'controller' therapy and may therefore be administered for relatively long periods of time. It is therefore possible that patients receiving omalizumab become infected with helminth parasites. The risk of becoming infected whilst receiving omalizumab is based on helminth exposure risk and therefore similar to that described in Table 4. During longer-term therapy, the risk of exposure to helminth infection may change on account of relocation. Repeated screening is unlikely to provide clinical benefit except perhaps in patients with high risk of filarial, schistosome or *Strongyloides* infection if potential exposures continue. Similarly if potential exposures are still present, treating physicians should consider a differential diagnosis of helminth infection in patients presenting with the relevant symptoms or laboratory findings. In patients who experience a helminth infection whilst receiving omalizumab, the infection should be immediately treated and patients followed-up accordingly.

Conclusion

There is little consistent evidence to indicate that IgE is a primary effector mechanism in protective immunity against helminth parasites including geohelminths, although it may be involved. Observational human data support the idea that protective mechanisms against helminth infections are multifactorial, and that the specific depletion of IgE should not unduly affect the host's ability to respond to these parasites.

Omalizumab is targeted for the treatment of patients with severe (and, in the USA, moderate) allergic asthma. These patients are typically on high systemically active doses of inhaled steroids and in addition some receive oral steroids. The impact of the broader immunosuppressive effects of steroids on parasite infections is not established but it is reasonable to assume that these effects of oral steroids in particular may increase risk of helminth-associated morbidity in this patient group. The risk with respect to omalizumab is not established, but omalizumab has been shown to displace the need for oral steroids in patients with the most severe forms of asthma.

The study by Cruz et al. 2007 (38) did not provide significant data on safety with respect to infections with strongyloidiasis or systemic helminth infections such as schistosomiasis. However, the study was conducted in a population considered to be at high risk of infections with ascariasis and trichuriasis and does provide some evidence that omalizumab therapy may not be associated with clinical morbidity caused by these common geohelminth parasites. Because of the significant difficulties in recruiting allergic patients at high risk of geohelminth infections in this study, it would appear unlikely that future intervention studies in other populations will be considered. Future observational studies could focus on the risk of infections with specific helminth parasites (importantly *S. stercoralis*) in allergic patients receiving different treatment regimens including anti-IgE and examine the effects of anti-IgE on *in vitro* immune responses. Important data are likely to accrue also from postmarketing surveillance of anti-IgE in countries where helminth infections are endemic.

The usefulness of screening for helminth infections before considering omalizumab therapy varies widely between different exposure risk groups, and is generally not necessary except in individuals with continuing exposure, a past history of filarial or schistosome infection, and individuals with a history or high risk of infection with *Strongyloides*. The findings of a possible increased risk of intestinal helminth infection in high-risk individuals receiving omalizumab treatment are consistent with a protective role for IgE. However, the presumed risk is relatively modest, lending support to a noncritical role for IgE in protective immunity against helminth parasites. Although IgE may have a role in the early amplification of anti-helminth immunity the role of IgE in protective immunity against helminth parasites is unlikely to be critical. Immunoglobulin E may function as one of many immunological factors within a multicomponent type-2 immune response.

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