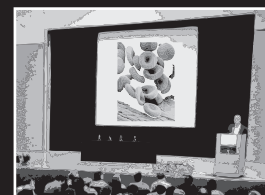


Conference Scene



Parasites to treat immune-mediated diseases?

2012 Annual Meeting of the American Academy of Allergy, Asthma & Immunology
Orlando, FL, USA, 2–6 March 2012

A growing number of childhood diseases, such as allergic disorders (e.g., allergic rhinitis, atopic dermatitis and asthma) and other immune-mediated diseases (e.g., Type 1 diabetes), have been linked to environmental exposures during prenatal and early postnatal life, along with genetic determinants. Immunological mechanisms, diagnosis, treatment, prevention and management of allergies and other immune-mediated diseases were discussed at the 2012 Annual Meeting of the American Academy of Allergy, Asthma & Immunology in Orlando, FL, USA, 2–6 March 2012.

Clinicians, academics and allied health professionals from all over the world met at the 2012 Annual Meeting of the American Academy of Allergy, Asthma & Immunology (AAAAI) in Orlando, FL, USA, 2–6 March 2012. A central theme discussed in multiple sessions was the role of the environment and ‘dirt’ in the occurrence of atopic diseases. This topic was covered by two different courses, entitled “Allergens and ‘dirt’: molecular pathways and consequences for the allergic epidemic (part 1 and 2),” both on 2 March, in addition to a symposium on 3 March entitled “Bacteria and viruses: fighting dirty,” and a seminar on 5 March entitled “Are we ready to use parasites to treat allergic diseases?” The latter session focused on the possible treatment of allergy and autoimmune diseases using parasites or molecules from parasites, and researchers with different expertise in the field were invited to share their data and discuss this topic.

The ‘hygiene hypothesis’, first postulated by Strachan in 1989, attempted to explain the temporal trends over recent decades of an increase in allergic disease prevalence in industrialized countries by alterations in the host response to environmental allergens caused by decreased exposure to childhood infections through improvements in hygiene and greater access to antibiotics and vaccines [1]. Intestinal helminth infections are of particular interest because they have strong immune regulatory effects on their host [2], continue to be highly prevalent in developing countries, are estimated to infect one-quarter of humans worldwide and typically occur in infancy [3]. The

most common helminth infections are caused by geohelminths (also known as intestinal and soil-transmitted helminths). Geohelminth parasites include *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm (*Ancylostoma duodenale* and *Necator americanus*); they have a worldwide distribution and are most prevalent among children living in areas of the rural tropics with poor access to sanitation and clean water. Other important helminth infections include schistosomiasis and filariasis, which have a more focal distribution within endemic countries [4].

Studies performed in Brazil [5–7] and those carried out in rural communities in Ecuador [8,9] suggest a protective role of parasites in decreasing skin test reactivity and the attenuation of asthma symptoms, particularly in infections with *Schistosoma* spp. In addition, intervention studies have provided support for a causal association between helminth infection and atopy [10]. By contrast, we and others have demonstrated that intestinal helminths such as *A. lumbricoides* and *T. trichiura* are associated with regulation of the immune response [2] and suppression of atopy [3], while other intestinal helminths have shown no effect on [9] or even an exacerbation of [11] atopic diseases. These discrepancies have been attributed to the timing of the infection in the human host, worm burden and the chronicity of such infections [12].

Short-term application (12 months) of antihelminth drugs in Ecuador [13] demonstrated no change in the prevalence of atopy, or clinical signs of allergy (wheeze) in comparison with an untreated group. However, long-term antihelminth

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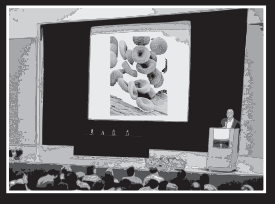
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treatment in Venezuelan children (age >22 months) and Gabonese children (age >30 months) resulted in increased skin prick test reactivity to house dust mite, supporting a direct link between chronic and intense helminth exposure and protection from allergy [12]. In fact, several physicians during the AAAAI seminar described how their patients' allergic symptoms worsened when they were treated for parasitic infections, and how their patients reported worse symptoms when they migrated to a developed country (unlikely to be endemic for helminths).

However, observations from recent clinical trials referred to by the speakers have failed to confirm the usefulness of live helminth infections in the treatment of immune-mediated diseases. For instance, the first randomized, double-blind, placebo-controlled study of the effects of experimental hookworm infection in patients with asthma was conducted by Feary *et al.*, and, although the infection was well tolerated, experimental infection with ten hookworm larvae did not result in significant improvement in bronchial responsiveness or other measures of asthma control [14]. It was suggested in that study that additional protocols that more closely mimic natural infection (e.g., trickle or repeated low-dose infections) are feasible and should be undertaken.

Research testing the potential of hookworm *N. americanus* to suppress the immunopathology induced by gluten was carried out in a double-blind, placebo-controlled study among a group of otherwise healthy people with celiac disease. Experimental *N. americanus* infection proved to be safe, which enabled testing of its effect on a range of measures of the human autoimmune response; however, the infection resulted in no obvious benefit on pathology [15]. It was reported in another clinical trial that subjects who ingested 2500 *Trichuris suis* eggs experienced significant gastrointestinal reactions, such as moderate-to-severe flatulence, diarrhea and upper abdominal pain, compared with placebo group [16].

Explanations for why clinical trials have failed so far, according to the seminar panel, include the following:

- Safety: doses used in clinical trials, which are considered to be safe, do not adequately mimic typical infection and are insufficient to protect from the disease;
- Chronic rather than current infections: the clinical trials conducted to date have evaluated the impact of short-term infections lasting a few weeks; however, epidemiological data suggest chronic helminth infection over years may be necessary [17];
- Prophylaxis: prevention instead of treatment may be the way in which parasites act and so infections in early childhood in endemic regions may be critical for the induction of protective effects.

Considering the issues listed above, the isolation of molecules from parasites appears to be a novel route for the development of new immunotherapies and is a strategy that avoids the experimental infection of human subjects. Several international groups have been studying molecules from parasites, such as *Schistosoma mansoni* antigens [18]. The main candidates are molecules that can induce regulatory cytokines, such as IL-10 and TGF- β , and may be more likely to control abnormal responses.

Although helminth infections are implicated in protecting the host against immune-mediated diseases, they are also believed to cause significant morbidity in endemic areas through their effects on nutrition, growth and cognition; they affect children's performance at school and have deleterious effects on vaccine immune responses [19]. Thus, it might be more practical to focus on individual helminth-derived immunomodulatory molecules to selectively induce regulatory immune responses (particularly those expressed during the chronic phase of infection) and avoid any possible side effects of natural worm infections. A few molecules have already been identified as potential candidates for immunotherapy. It is important that efforts continue to bring these molecules to the clinical setting, preferably coupled with allergens to target allergen-specific changes and allow low concentrations to be effective.

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