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SPECIAL SUPPLEMENT

ATOPIC MARCH AND DISEASE MODIFICATION

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Dr. Adam Byrne is originally from St. John's, Newfoundland, where he graduated from Memorial University with a M.Sc. in Biochemistry. He worked on several research projects afterwards at Memorial University, including the metabolism of adipose tissue before moving to novel detection of HPV infection at Newfoundland Public Health Labs. He returned to medical school at Memorial University before completing his Pediatrics residency at the University of Ottawa. He completed a fellowship in Pediatric Clinical Immunology and Allergy at McGill University before returning to Ottawa, where he now practices Allergy and Immunology in private practice in the community, as well as at the Children's Hospital of Eastern Ontario, where he was the recipient of the award for clinical excellence in his first year of practice. Dr. Byrne is a member of various societies, and is a member of the CSACI, where he is active in education as a co-chair of the National Residency Education Program and a member of the Committee for Professional Development.

ATOPIC MARCH AND DISEASE MODIFICATION

ABBREVIATIONS

AD: atopic dermatitis, **AR:** allergic rhinitis, **EoE**: eosinophilic esophagitis, **IgE**: immunoglobulin E, **TSLP**: thymic stromal lymphopoietin, **ILC2**: type II innate lymphoid cell, **STAT**: signal transducer and activator of transcription

INTRODUCTION

Over generations of health care providers, the approach to medicine has predominantly been reactive in nature, addressing symptoms as they arise. With advancements in medical research that explore the underlying mechanisms of disease, associated comorbidities, and improved therapeutic options, the objectives of medicine are transforming. While managing active symptoms remains crucial, there is a growing focus on altering the future trajectory of a disease which will result in new avenues to improve the quality of life of patients. In this evolving landscape, the atopic march emerges as a promising area for disease modification.

ATOPIC MARCH

A steady rise has been noted in the diagnosis of atopic conditions worldwide. For example, in Canada, estimates for the prevalence of food allergy are as high as 7.5%,[1] while the prevalence of allergic rhinitis (AR) can reach 20–25% in the general population.[2] Atopic dermatitis (AD), the first presentation associated with the development of atopy, has been reported in 10–20% of Canadians.[3] Some of these patients will demonstrate "the atopic march", which is the term used to describe the stepwise progression of atopic disease in an individual. The atopic march starts with AD, typically around 6 months of age. Patients then develop immunoglobulin E (IgE)-mediated food allergy, usually around the age of 1–2 years old, before developing allergic asthma and rhinitis later in childhood.[4] Not all patients with atopic conditions experience progression of the atopic march. A recent study indicated that only 10% of individuals with atopic conditions manifest the complete spectrum of associated diseases.[5] However, the presence of food allergy early in life increases the risk of developing at least one additional atopic condition.

The findings of many studies support the concept of the atopic march. An Italian study demonstrated that infants diagnosed with moderate-to-severe AD were more likely to develop allergic asthma. The same study also demonstrated that patients who had developed allergic asthma were more likely to develop AR.[6] The Canadian CHILD cohort study demonstrated that AD at

1 year of age with allergic sensitization was associated with an increased risk of allergic asthma and food allergy.[7] Notably, AD alone was not associated with an increased risk of asthma. A Japanese retrospective study found that IgE-mediated food allergy had the highest risk for progression along the atopic march, which had strong associations with AD, asthma, and AR.[8] This study went on to demonstrate that food allergy was associated with younger age at presentation of AD.

Recent evidence suggests that a fifth atopic presentation, eosinophilic esophagitis (EoE), may be a late addition to the atopic march. A case-control analysis in children demonstrated that early diagnosis of AD, asthma, and AR increased the risk of a diagnosis of EoE.[4] Genome wide association studies have linked mutations in signal transducer and activator of transcription 6 (STAT6) and thymic stromal lymphopoietin (TSLP) to both AD and EoE.[9] Further research in this area is required to confirm this association.

ATOPIC MARCH: PATHOPHYSIOLOGY

There are multiple proposed mechanisms that contribute to the unifying pathophysiology behind the atopic march. Several excellent reviews on this topic have been published.[10-12] A brief summary of these reviews is provided below.

The onset of the atopic march is likely initiated by a disruption in skin function. Intact skin includes a layer of cornified keratinocytes, which serve as a vital barrier to prevent the infiltration of external antigens into the body. In AD, this barrier becomes compromised owing to mutations in genes such as FLG, responsible for the production of filaggrin, a pivotal protein crucial for both keratinocyte aggregation and barrier formation. The compromised integrity of the skin allows antigens and irritants to breach the barrier, prompting keratinocytes to release cytokines such as TSLP, interleukin (IL)-33, and IL-25. Notably, FLG mutations are also linked to staphylococcus colonization, and evidence suggests that exposure to staphylococcal superantigens, particularly in conjunction with exposure to peanut allergens, heightens the risk of developing an IgE-mediated food allergy to peanuts.

Mutations in the TSLP gene are common in AD, resulting in overexpression of the TSLP protein. TSLP is an IL-7-derived cytokine, that in conjunction with IL-25 and IL-33, predisposes a shift in the immune system to a T helper 2 (Th2) inflammatory pattern. Specifically, TSLP induces type II innate lymphoid cells (ILC2) to produce IL-5 and IL-13, which are drivers of eosinophilic recruitment. TSLP also activates dendritic cells and naïve T-cells to shift towards Th2 cells, resulting in the production of more IL-4, IL-5, and IL-13. IL-5 plays a crucial role in increasing eosinophilic concentrations through enhanced recruitment and survival, while IL-4 and IL-13 result in the transition of naïve T-cells to Th2 cells and further type 2 inflammation, including activation of B-cells with associated class switching to specific IgE. Next, this IgE then binds to mast cells and basophils. Upon the next exposure to the target antigen, cross-linking of IgE on IgE-receptors results in activation of the mast cells and basophils, leading to the classic symptoms of IgE-mediated food allergy, AR, and asthma. The IL-4 and IL-13 cytokines are also involved in further barrier disruption, with IL-13 being associated with tissue remodelling for both airways in asthma and the esophageal lining in EoE. A full representation of this process is illustrated in **Figure 1**.

Considering that the atopic march is multifactorial, other causes likely contribute to the pathophysiology, such as epigenetics and altered microbiomes, which are beyond the scope of this review.

ATOPIC MARCH: DISEASE MODIFICATION

For most diseases that can be modified via therapeutic intervention, the timing of the intervention often strongly influences the results. Outcomes are generally thought to be more effective when introduced early in the process rather than later. This approach is even more important in the atopic march, in which early identification of high-risk patients, particularly those with AD with an appropriate response to treatment, would ideally prevent the development of further atopic conditions. Gaining an understanding of the trajectory and mechanisms behind the atopic march has provided medicine with tools to attempt to alter its progression.

Optimal therapeutic outcomes may involve achieving atopic disease remission, whereby the patient can lead a normal quality of life with their active atopic disease while also further preventing new diseases from occurring. It should be noted that remission in this context does not 'cure' the patient of their active issue, especially considering that chronic atopic diseases such as AD may involve recurrent flaring of symptoms. The primary objective of disease modification within the atopic march is identifying the early stages and initiating interventions to arrest progress.

Later interventions are often less successful and carry more risks, which is best demonstrated by oral immunotherapy for food allergy. The LEAP study demonstrated that early introduction of peanut protein in the diet, both in low and high-risk patients as indicated by AD or egg allergy, was an effective measure to reduce the risk of IgE-mediated allergies to peanuts. Notably, findings from the LEAP study resulted in a change in our food allergy guidelines.[13] Evidence has shown that older patients may not achieve the desired level of tolerance for oral immunotherapy, and

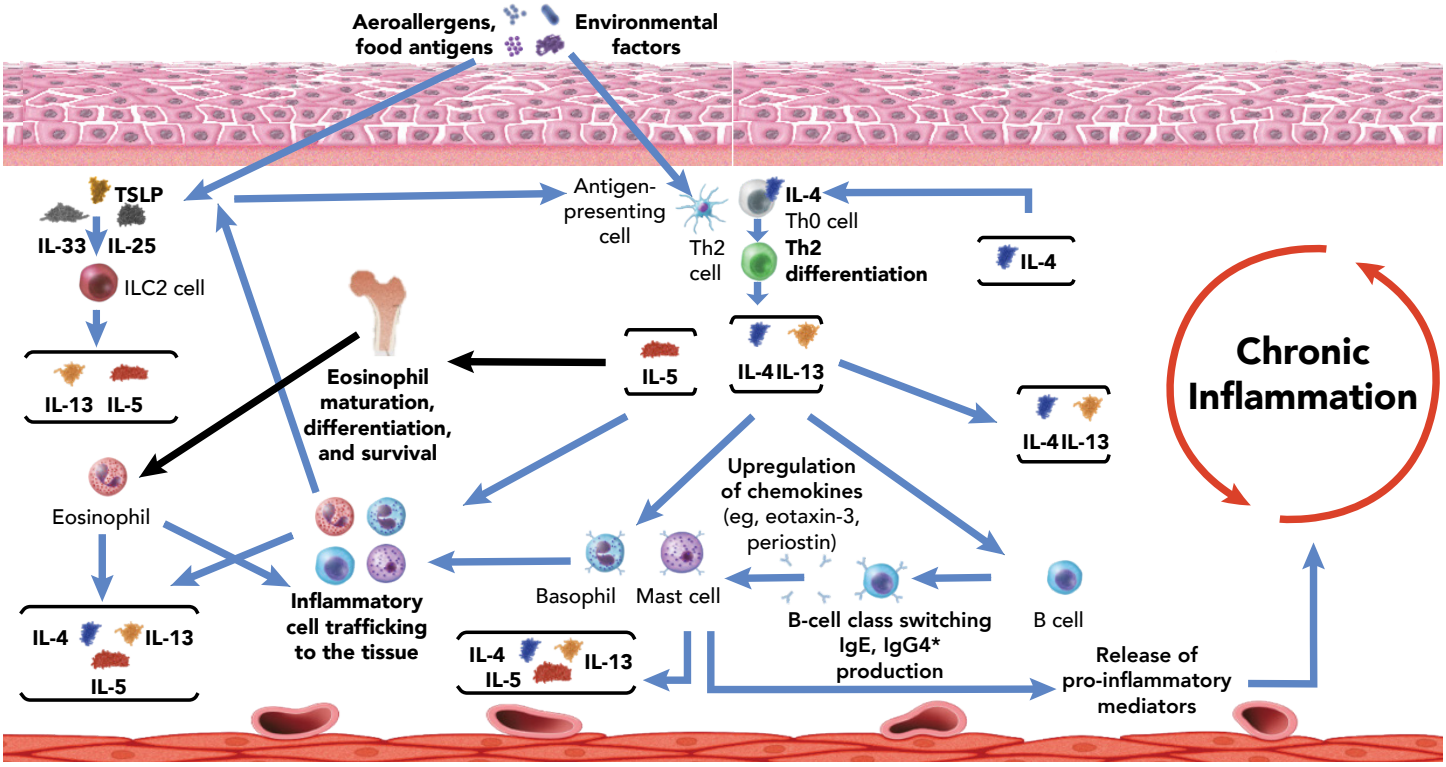

Figure 1. A Model of Barrier Dysfunction, Type 2 Inflammation, and the Atopic March.
Abbreviations: IgE: immunoglobulin E, **IgG4:** immunoglobulin G4, **IL:** interleukin, **ILC2:** type 2 innate lymphoid cell, **Th:** T helper, **TSLP:** thymic stromal lymphopoietin.

quite frequently have increased side effects during the treatment process compared with younger children.[14] These reports of success with early intervention suggests that the immune system is more malleable at a younger age, providing evidence that earlier interventions can modify the natural history of the atopic march.

Other interventions have attempted to alter AD outcomes through repair of the barrier function of the skin. The aim of the PEBBLES study was to examine whether application of a ceramide-containing emollient twice daily could reduce the risk of AD and food allergy development in patients considered at high risk owing to a family history of atopy. In addition to physical assessments at 6 and 12 months of age, other assessments included transepidermal water loss and skin prick testing to 6 common allergens. In the per protocol analysis that followed, there was a significant reduction in food sensitization at 12 months in the treatment group compared with the control group.[15] However, a subsequent Cochrane analysis on the use of emollients for prevention of atopy found no significant effect, with a potential increase in the risk of skin infections,[16] indicating further research is still required.

The Prevention of Allergies via Cutaneous Intervention (PACI) study[17] aimed to improve outcomes for food allergies in infants with AD. Infants aged 7–13 weeks old were randomly assigned to a standard or enhanced treatment group, in which the standard treatment was reactive use of topical steroids for eczema flares, while the enhanced protocol involved proactive topical steroid application. The enhanced treatment group demonstrated a 10% decrease in hen's egg allergy development. However, infants in the enhanced group had lower weight and height gains compared with those in the standard treatment group, suggesting that the side effects of regular steroid use might be impractical for real-world settings.

Efforts have been made to modify the risk factors associated with AR and asthma. Several studies have examined immunotherapy for environmental triggers in high-risk patients, along with the effects of this therapy on asthma development. One study looked at 1 year of treatment with house dust mite sub-lingual immunotherapy (SLIT) tablets in infants. The study went on to follow up with these patients at 6 years of age and found a significant decrease in the number of asthma diagnoses in the group treated with immunotherapy.[18] In addition, grass pollen sublingual immunotherapy in patients with a grass allergy delayed the rate of diagnosis of asthma in the treated group while also decreasing the severity of the disease.[19]

ATOPIC MARCH: FUTURE RESEARCH IN DISEASE MODIFICATION

One of the factors that is known to contribute to the development of atopic conditions, especially asthma, is respiratory viral infection.[20] Infections such as rhinovirus and respiratory syncytial virus can lead to an escalation of Th2 responses in susceptible individuals. Omalizumab is a recombinant monoclonal anti-IgE antibody that effectively binds and eliminates free IgE. Omalizumab is approved for management of chronic spontaneous urticaria, moderate-to-severe asthma, and chronic rhinitis with nasal polyps. Research has demonstrated that treatment of asthmatic children with omalizumab reduces the number and severity of exacerbations, especially during respiratory viral seasons, likely through the increased efficiency of interferon-α.[21] These observations have laid the groundwork for the PARK (Prevention of Asthma in high-Risk Kids) study,[22] which aims to assess whether treatment with omalizumab in children aged 2–3 years old can prevent or mitigate the development of asthma later in life. The study's current objective involves treating children with omalizumab for approximately 2 years, followed by 2 years of follow-up for symptom progression. Results from this study have not yet been reported.

In children and adults, the use of dupilumab also provides another potential disease modifying agent. Dupilumab is a monoclonal antibody that binds to the IL-4 receptor-α and is approved for management of moderate-to-severe AD, severe asthma, severe chronic rhinosinusitis with nasal polyposis, and EoE. Dupilumab decreases the production of inflammatory cytokines IL-4 and IL-13. In patients with AD, dupilumab decreases the mRNA expression of genes that cause hyperplasia, and genes involved in the production of T-cells and dendritic cells, which can lead to an associated improvement in skin quality.[23] In addition, treatment with dupilumab has shown a marked improvement in transepidermal water loss in AD patients, which is also associated with an improvement in clinical symptoms.[24] Dupilumab treatment has also been shown to alter the microbiome of the skin, including decreased colonization of staphylococcal species.[25] Dupilumab has recently been approved for the management of moderate-to-severe AD in patients aged 6 months and older based on the findings of studies that have demonstrated its safety and efficacy for these patients.[26] As dupilumab is used in younger patients to treat AD, studies will continue to follow these patients to determine if this intervention not only changes the outcomes of AD, but also the development of the rest of the atopic march as well, such as in the PEDISTAD study, a longitudinal study of pediatric patients with moderate-to-severe AD receiving any form of systemic therapy.[27] Initial review of the existing data shows promise, as seen in a meta-analysis looking at the development of further atopic disease development in patients treated with dupilumab at a young age, with an estimated 37% reduced risk of new allergy diagnosis.[28]

CONCLUSIONS

Patients who experience the atopic march have diseases that result in significant health risks and a lower quality of life. Gaining a better understanding of the pathophysiology of the atopic march is leading to the development of treatments that will address the symptoms of the active stage of the atopic march and prevent further progression. The advent of personalized medicine in the age of biologics holds promise for patients with atopic conditions. These patients will have access to more disease modifying options in the future.

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Dr. Byrne has received an honorarium for this manuscript.

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