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# The Emerging Role of the Type 2 Inflammatory Cascade in Atopic Diseases

**ATOPIC DISEASES POSE A** considerable and growing public health burden, affecting millions of patients worldwide, with the greatest impact on children and young adults. Often, multiple atopic conditions coexist in affected patients,<sup>1</sup> which suggests that an integrated approach to diagnosis and treatment may be beneficial for both patients and healthcare practitioners. Recent research and development of new pharmacologic agents to treat allergic conditions have focused on the type 2 inflammatory response, which is a pathologic process common to several inflammatory and infectious conditions.<sup>2</sup> Type 2 inflammation is characterized by high levels of immunoglobulin E (IgE) and eosinophils and is regulated by certain immune mediators.<sup>3</sup>

This article reviews the clinical and economic burden of asthma, atopic dermatitis (AD), and chronic rhinosinusitis with nasal polyps (CRSwNP), all of which are type 2 inflammatory diseases. It also explores the type 2 inflammatory cascade in each of these conditions and the basis for type 2 inflammation as an underlying process in atopic diseases more generally.

## The Clinical and Economic Burden of Atopic Diseases *Asthma*

Asthma is a chronic respiratory condition that affects patients across the lifespan, from childhood to old age.<sup>4</sup> Patients with asthma experience exacerbations, which are periods of reversible airway obstruction that lead to symptoms such as chest tightness, coughing, wheezing, shortness of breath, and sputum production.<sup>4-6</sup> In the past, asthma was viewed as a single disease entity characterized by airway inflammation, reversible airflow obstruction, and bronchial hyperresponsiveness.<sup>7,8</sup> Over time, however, this understanding has evolved. Asthma is now recognized as a heterogenous disease that varies in etiology, symptom triggers, clinical presentation, and response to treatment.<sup>9,10</sup> In particular, recent evidence points to defective epithelial barrier function and junctional complexes as a prominent feature of airway inflammation in asthma.<sup>11</sup>

Worldwide, asthma is the most common chronic lung disease, affecting an estimated 300 million individuals.<sup>2,4</sup> According to recent statistics, 25.2 million patients in the United States currently have a diagnosis of asthma, including 19.0 million adults (1 in 13) and 6.2 million children (1 in 12).<sup>12</sup>

Uncontrolled asthma is associated with diminished productivity and quality of life (QoL) and increased healthcare utilization, which all translate to considerable economic costs.<sup>6,13</sup> In terms of lost productivity, asthma leads to the loss of 1.8 workdays and 2.3 school days per person per year, which costs an estimated \$3 billion each year in the United States.<sup>6</sup> Healthcare utilization related to asthma is substantial. In 2010, asthma contributed to 10.6 million physician visits, 1.2 million hospital outpatient department visits, and 2.1 million emergency department (ED) visits.<sup>14</sup> The total yearly cost of medical care for asthma in the United States is on average \$50.3 billion.<sup>6</sup> Mortality due to

asthma is also substantial, with estimates of nearly 3200 deaths in the United States and at least 250,000 deaths worldwide attributable to asthma each year.<sup>2,4,6</sup> Asthma-related deaths in the United States translate to about \$29 billion in yearly costs.<sup>6</sup> Combining the estimated costs for lost productivity, medical care, and death, the total annual economic burden of asthma in the United States is roughly \$81.9 billion.<sup>6</sup> Coordination of care among providers, payers, and patients to optimize outcomes for patients with asthma has the potential to decrease the economic burden of asthma.

### *Atopic Dermatitis*

AD is a chronic disease characterized by relapsing inflammatory skin lesions and itching. Genetic and immunologic factors have been identified in the pathology of this disease.<sup>15</sup> The incidence of AD has increased 2- to 3-fold over the past 30 years, affecting 15% to 20% of children and 1% to 3% of adults worldwide.<sup>15,16</sup> Notably, the incidence of AD is lower in rural areas and in nonaffluent countries, suggesting that lifestyle and environmental factors may play an important role in disease onset.<sup>15</sup> Symptoms of the disease typically present in early stages of life and resolve with age; however, a significant number of adults live with AD.<sup>16</sup> The onset of AD in children occurs in 45% during the first 6 months of life, 60% during the first year, and 85% before age 5 years.<sup>15</sup>

AD can have a significant impact on QoL. The primary symptom of itching, for instance, can lead to sleep disturbances and poor behavior in children. Additionally, AD also affects the QoL of parents and caregivers, suggesting a family-wide burden experience.<sup>16</sup> Given the amount of direct and indirect costs of AD, the economic burden of the disease is difficult to quantify.<sup>16</sup> Direct costs include prescription and nonprescription medications, healthcare provider visits, and hospital and ED visits, while indirect costs include absenteeism from work, school, and physical activities. Notably, doctor visits and increased prescription and over-the-counter medication costs contribute to the financial impact of the disease.<sup>16</sup> The average personal cost of AD in the month before an office visit (including direct and indirect costs) is roughly \$274 per patient (\$75 direct costs; \$199 indirect costs).<sup>17</sup>

### *CRSwNP*

CRSwNP is characterized by inflammation of the nose and paranasal sinuses with the presence of polyps.<sup>18</sup> Nasal polyps affect approximately 1% to 4% of the US population and are typically associated with chronic

rhinosinusitis. In patients with CRSwNP, the nasal polyps are benign, yet the disease is associated with significant morbidity and a lower QoL. The disease is typically diagnosed in middle-aged patients, with more men than women diagnosed. To date, no genetic or environmental factors have been linked to the development of the disorder.<sup>18</sup>

Although the mechanisms of inflammation are not well defined, one hypothesis suggests that an impaired sinonasal epithelial barrier leads to increased exposure to inhaled pathogens, antigens, and particulates that could promote chronic inflammation.<sup>18</sup> Additionally, sinonasal epithelial barrier dysfunction leads to increased tissue permeability and decreased epithelial resistance, which may be attributed to abnormal cells and/or extrinsic factors.<sup>18</sup> Other epithelial defense mechanisms may also be impaired, which can lead to a decrease in mucociliary clearance, reduction in antimicrobial defense protein secretion, and breakdown in the physical barrier.<sup>18</sup> Bacteria and fungi may also play a role in epithelial dysfunction.<sup>18</sup>

### *The Pathway of Type 2 Inflammation*

The type 2 inflammatory pathway occurs in response to atopic diseases, including asthma, AD, and CRSwNP, as well as to certain parasitic infections.<sup>4</sup> Following exposure to an allergen, dendritic cells present the antigen to naïve CD4+ T cells, which differentiate to form mature type 2 helper T cells (Th2 cells). Th2 cells, in turn, secrete numerous cytokines, especially interleukin-4 (IL-4), IL-5, IL-9, and IL-13 (**Figure**).<sup>7</sup> IL-4 and IL-13 facilitate the production of IgE from B cells<sup>19</sup> and are also strongly associated with barrier dysfunction.<sup>20</sup> IL-5 stimulates production of eosinophils in the bone marrow, as well as activation and movement of eosinophils and basophils, while IL-9 stimulates the production of mast cells in the bone marrow.<sup>5</sup> Via this pathway, type 2 inflammation is thus characterized by tissue infiltration by eosinophils and basophils, as well as by mast cell degranulation.<sup>5</sup> Historically, pharmacologic treatments for many allergic conditions exert their effects further down the type 2 inflammatory cascade, but more recent developments in targeted therapies have demonstrated efficacy in the management of allergic disease.<sup>7</sup>

### *Asthma*

Two major hallmarks in patients with atopic asthma are the presence of high levels of IgE and eosinophils, as their production is the result of the type 2 inflammatory process.<sup>9</sup> As described previously, the type 2

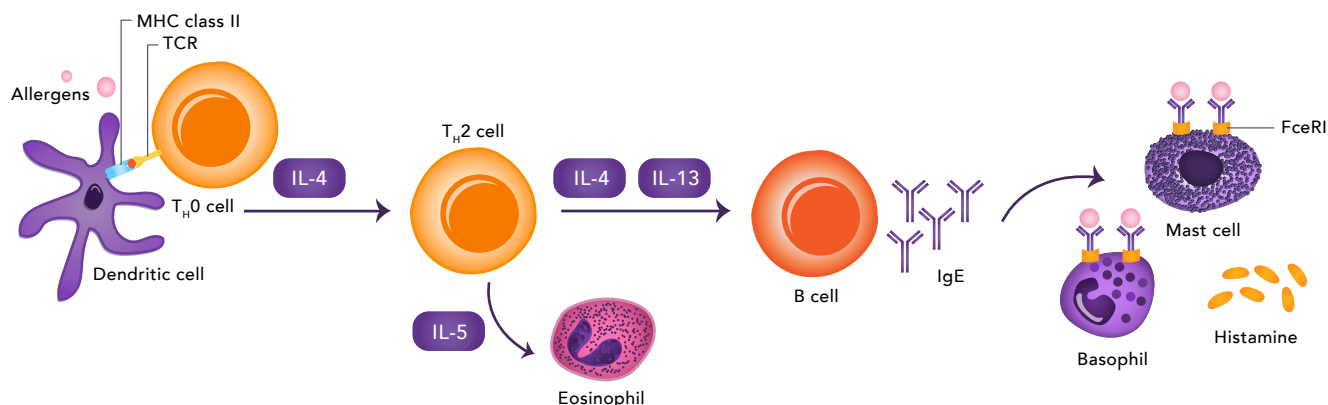
**FIGURE.** The Type 2 Inflammatory Cascade and Selected Pharmacologic Agents<sup>7</sup>

Figure adapted from Gandhi NA, Bennett BL, Graham NM, Pirozzi G, Stahl N, Yancopoulos GD. Targeting key proximal drivers of type 2 inflammation in disease. *Nat Rev Drug Discov.* 2016;15(1):35-50.

inflammatory cascade is activated in response to atopic asthma.<sup>9</sup> In general, type 2 inflammation of the airway is characterized by accumulation of Th2 cells, type 2 innate lymphoid cells, B cells that produce IgE, type 2 cytokines (ie, IL-4, IL-5, and IL-13), and effector cells (ie, eosinophils, basophils, and mast cells), which have been implicated in the pathogenesis of asthma exacerbations. Importantly, epithelial barrier dysfunction caused by environmental exposures may be linked to Th2 polarization.<sup>11</sup>

Upstream in the type 2 inflammation pathway in the airway, several primary regulators called alarmins, including IL-25, IL-33, and thymic stromal lymphopoietin, are released following an environmental insult by an allergen, pollutant, or virus. These alarmins set off the type 2 inflammatory cascade, facilitating maturation of CD4+ T cells into Th2 cells and stimulating the overproduction of IL-4, IL-5, and IL-13; this in turn attracts effector cells and drives the activation and remodeling of the airway epithelium and subepithelial tissue. Via these changes, the type 2 inflammatory cascade is thought to predispose patients to an amplified response to inhaled exacerbants.<sup>3,9</sup>

More recent research has focused on evaluating patients with atopic asthma based on expression of Th2 cells and type 2 cytokines. As a result, patients may now be further subclassified into 2 possible endotypes (eg, distinct diseases): Th2-high and Th2-low. The Th2-high asthma endotype, which is present in about 50% of patients with atopic asthma, is distinguished by greater bronchial hyperresponsiveness, higher levels of systemic and airway eosinophilia, and response to corticosteroids and inhibitors of the type 2 inflammatory pathway. The Th2-low asthma endotype is believed to represent several smaller, distinct endotypes, but additional research is needed to better understand the

inflammatory processes underlying atopic asthma in this patient group.<sup>3,4</sup>

In atopic asthma, IL-4 is the key driver in the differentiation of CD4+ T cells into Th2 cells, and IL-4 also stimulates the production of both IL-5 and IL-13.<sup>7</sup> IL-4 and IL-13 facilitate the switching of B cells to IgE.<sup>7</sup> IL-5 and IL-13 are central to the pathophysiology of atopic asthma, contributing to bronchial hyperresponsiveness, airway remodeling, mucus production, and synthesis of IgE.<sup>9</sup> IL-5 modulates the development, maturation, and accumulation of eosinophils, as well as the development and function of basophils and mast cells.<sup>3,9,10</sup>

Numerous pharmacologic agents targeting various points in the type 2 inflammatory cascade are currently in development or have already been approved for the treatment of atopic asthma, especially in patients with Th2-high asthma endotype. One of the first targeted agents approved for the treatment of atopic asthma was omalizumab, which works primarily by depleting IgE and blocking its effect on dendritic cells.<sup>4</sup> Agents that selectively bind to and block IL-5, including mepolizumab and reslizumab, inhibit eosinophilic inflammation and have demonstrated reductions in asthma exacerbations among patients with persistent eosinophilia despite other treatments.<sup>3</sup> Other recent developments in targeted therapy include agents that selectively bind to and block either IL-13, including lebrikizumab and tralokinumab, or IL-4, including altrakincept; other agents more broadly inhibit the activity of both IL-4 and IL-13, such as dupilumab and pitrakinra.

### Atopic Dermatitis

Importantly, not all atopic diseases are triggered by allergens or allergic exposure. The pathology of AD is multifaceted. It is a complex, chronic inflammatory

disease process. Often preceding the onset of other inflammatory conditions, such as food allergy, asthma, and allergic rhinitis, AD is a systemic disease.<sup>21</sup> Skin lesions have shown increased numbers of inflammatory cells including T-helper cells, IgE plasma cells, eosinophils, and mast cells.<sup>22</sup> One hallmark of AD is skin barrier dysfunction, which leads to increased water loss and allows for the penetration of noxious environmental stimulants, in turn triggering the immune response pathway.<sup>22</sup> Barrier dysfunction in AD-affected skin can be attributed to a deficiency of filaggrin, along with other abnormalities. Filaggrin loss is associated with poor skin hydration and enhanced penetration of allergens through the skin.<sup>21</sup>

Early immune response has been found to be type 2-mediated, with AD skin having a high expression of IL-4, IL-13, IL-25, and IL-33.<sup>22</sup> IL-4 and IL-13 stimulate eosinophil recruitment, IgE class switching, and induce Th2 cell survival and activation.<sup>22</sup> IL-4 and IL-13 also play a role in keratinocyte differentiation and down-regulate the production of filaggrin and cell adhesion molecules, leading to a defective skin barrier.<sup>22</sup> The immune response has been confirmed by findings which show that patients with severe AD experience significant improvement when treated with dupilumab, a humanized antibody that inhibits IL-4 and IL-13 and was approved by the FDA in 2017.<sup>23</sup> IL-23 appears to play an important role in immune pathway activation of AD, as well, because it differentiates between Th17 and Th22 cells, both of which produce IL-22 and inhibit keratinocyte differentiation. Thus, early case reports suggest that inhibiting IL-23 can lead to improvement of severe AD.<sup>22</sup>

Importantly, significant heterogeneity has been observed in AD immune responses, with age, race, and severity of disease being associated with different patterns of immune activation. For example, severe types of AD are often characterized by selective expansions of circulating Th2 and Th22.<sup>23</sup>

### CRSwNP

The pathology of CRSwNP is complex and involves dysregulation of the host immune response as well as extrinsic factors. The most prevalent endotype of CRSwNP demonstrates a type 2 mediated inflammatory response and is characterized by a high prevalence of eosinophils, mast cells, and basophils, as well as elevated type 2 cytokines (IL-4, IL-5, IL-13, IL-25, and IL-33) and Th2 cells.<sup>18,24</sup>

Moreover, a defective epithelial barrier indicates a role for proinflammatory cytokines in the pathogenesis of the disease.<sup>25</sup> Thus, type 2 inflammatory involvement in CRSwNP is believed to have a driving role in the disease process.<sup>18,26</sup> This can be attributed to a lack of regulatory

T-cell function, local IgE production induced by IL-4 and IL-13, and eosinophilic inflammation induced by IL-4 and IL-13 as well as by IL-5.

### Conclusions

The chronic illnesses reviewed in this article have a common underlying pathology involving the type 2 inflammatory pathway, which may explain, in part, the frequency of these conditions coexisting with each other.<sup>1</sup> This is echoed by presence of barrier dysfunction in all of these diseases. In particular, IL-4 and IL-13 appear to be integral in the downregulation of filaggrin and epithelial resistance, both of which are critical drivers of barrier dysfunction.<sup>20,22</sup>

The involvement of this specific immune response allows for the premise of precision medicine to be applied to emerging treatment approaches. The next article in this publication will review the current and emerging therapeutics in type 2 inflammatory diseases, with an emphasis on targeting specific inflammatory pathways to enable more refined and efficacious approaches to disease management. ♦

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