REVIEW

Insights into the Implications of Coexisting Type 2 Inflammatory Diseases

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Abstract: The role of type 2 inflammation in the pathogenesis of certain human diseases is an area of active investigation. Certain asthma, atopic dermatitis, eosinophilic esophagitis, and chronic rhinosinusitis phenotypes are characterized by a Th2 predominant inflammatory pathway and are frequently associated with comorbid conditions in patients. The purpose of this article is to review the evidence behind concurrent Th2-mediated diseases and explore how the presence of these comorbid conditions affect patient and disease outcomes.

Keywords: type 2 inflammation, Th2 inflammation, asthma, atopic dermatitis, eosinophilic esophagitis, chronic rhinosinusitis

Introduction

Inflammation is classically thought to be the body's defense against infection or injury, thereby maintaining homeostasis.[1] The inflammatory cascade is directed by the innate and adaptive immune systems, which are thought to have 3 major classes of cell-mediated effector immunity. The role of type I immunity is primarily protection against intracellular microbes, while type 3 immunity plays a protective role against extracellular bacteria and fungi.[2] Recent investigations have suggested that both type I and type 3 immune responses may play a pathogenic role in some human autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, Hashimoto thyroiditis, inflammatory bowel disease, and others. Type 2 inflammation, long associated with protection against helminth infections is also suggested to play a pathogenic role in some human diseases.[2]

The type 2 inflammatory response is primarily driven by T-helper 2 (Th2) cells following the presentation of antigen to naïve T-cells. Complex signaling pathways drive Th2 chemotaxis toward the site of inflammation, and stimulate the production of cytokines important in the type 2 inflammatory cascade. Interleukin (IL) 4 promotes the differentiation of naïve Th cells into Th2 cells and is also vital in stimulating isotype class switching of B cells to produce IgE. IgE antibodies further advance the immune response by sensitization of basophils and mast cells. Additional signaling provided by IL-5 and IL-9 leads to eosinophil and mast cell recruitment to the site of inflammation, and IL-13 is engaged in goblet cell hyperplasia, mucus secretion, and airway responsiveness.[3] Recently, investigators have recognized that type 2 inflammation may also play a pathogenic role in atopic and other inflammatory diseases.

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Type 2 Inflammation in Chronic Disease States

Asthma

Asthma is a disorder resulting in chronic inflammation of the airways, leading to recurrent episodes of wheezing, chest tightness, and coughing.[4] Endotype driven classification of asthma has allowed researchers to understand the molecular basis behind inflammation in different subsets of asthma. As such, treatments may be specifically targeted for the relevant molecular mechanism.[5] Th2-related asthma is thought to make up about 50% of mild to moderate asthma.[6] These patients also tend to be more responsive to glucocorticoid therapy and tend to exhibit local and systemic eosinophilia. However, a subset of Th2 mediated asthma patients do not show significant response to glucocorticoid therapy either due to steroid resistance or significantly high levels of Th2 inflammation that is unable to be controlled with steroids.[5] This has led to the development of novel therapeutics targeting the molecular basis behind the inflammation. The advent of biologic therapies for the treatment of type 2 inflammatory diseases has significantly enhanced the outcomes of difficult to treat disease.

Eosinophilic Esophagitis

Eosinophilic esophagitis (EOE) is a disease characterized by esophageal dysfunction histologically associated with eosinophilic type inflammation. Characterized clinically with symptoms of dysphagia, heartburn, abdominal pain, and food avoidance, EOE is often initially misdiagnosed as gastroesophageal reflux disease (GERD).[7] However, it is important to understand that these are two distinct clinical entities with differing pathogenesis. Although the pathophysiology of EOE continues to be investigated, it is known that chronic, Th2 mediated inflammation seems to be a major contributing factor to disease propagation.[8] Genetic profiling has also suggested that EOE patients may be predisposed to the development of allergic and eosinophilic inflammation in the esophagus. The management of EOE, similar to other type 2 inflammatory diseases, relies on reducing the eosinophilic inflammation within the esophagus. Elimination diets and proton-pump inhibitors have been suggested as potential first-line therapies for the treatment of EOE; however, topical corticosteroids have been the mainstay of therapy.[8] While topical steroids tend to have great success with inducing remission of EOE, relapse typically occurs within a few weeks after cessation.[9,10] As with other Th2 mediated diseases, biologics targeting IL-5 and IL-13 are currently being investigated as potential treatment options. While trials have shown promise with reducing eosinophil counts and inflammatory markers, symptom improvement has been less predictable.[11–14]

Atopic Dermatitis (AD)

Atopic dermatitis is a chronic, relapsing inflammatory skin disease characterized by erythematous, pruritic patches. Classically considered a disease of children, it is now known that AD affects people of all ages, and it is estimated that upwards of 230 million people worldwide are diagnosed with AD.[15] Genetics, environmental exposures, and immunological factors may all have a role in the pathogenesis of AD and are currently being investigated. The inflammatory profiles of AD demonstrate a Th2 dominance during the acute phases of AD development.[16] Messenger ribonucleic acid (mRNA) encoding Th2-specific cytokines, IL-4 and IL-13, are greatly increased in acute lesions and may be involved in some skin barrier dysfunction further exacerbating the disease process.[17] The aims of management of AD are focused on establishing persistent disease control by avoiding triggers of disease exacerbations, improving the skin condition, and reducing the inflammation. Basic therapy that all AD patients should be educated on is focused on improving skin health with hydrating topical therapies, emollients, and occlusive dressings. For mild disease, topical corticosteroids continue to be the first-line treatment. Topical calcineurin inhibitors may be used in the short term in sensitive areas. Short-term phototherapy is an option when topical measures fail to achieve disease control. Systemic treatments including immunosuppressive agents, corticosteroids, and biologics are considered when the above measures fail.[15]

Chronic Rhinosinusitis (CRS)

Chronic rhinosinusitis is a disease of inflammation of the nose and paranasal sinuses characterized by at least 12 weeks of nasal congestion, facial pain or pressure, nasal discharge, and impairment of the sense of smell. CRS is estimated to affect nearly 10% of the adult population and results in significantly decreased quality of life, decreased productivity, and large financial impacts for disease management.[18] CRS was classically grouped based on the presence or absence of nasal polyps; however, recent understanding of the underlying inflammatory profiles (ie,

endotypes) of CRS has led some to suggest revising this classification scheme.[19] CRS with a Th2 endotype tends to be more associated with nasal polyps, smell loss, and allergic mucin, when compared to non-Th2 patients.[20] The management of CRS is largely based on appropriate medical management with surgery reserved for patients who do not respond to maximal medical therapy. The term maximal medical therapy has been used to describe a trial of nasal saline irrigations, topical corticosteroid sprays, antibiotics, and occasionally systemic corticosteroids.[21] Patients with a Th2 predominant endotype tend to be more responsive to corticosteroid therapy than non-Th2 patients, however, despite adequate surgery and appropriate medical therapy a subset of patients experience persistent disease. The introduction of biologics targeting the type 2 inflammatory pathway has shown promise in treating recalcitrant disease, similar to the other Th2 mediated diseases described above.[22]

Interplay Between Different Type 2 Inflammatory Diseases

As our understanding of type 2 inflammatory diseases continues to expand, the effect of co-existent diseases on patient outcomes will need to be investigated. The current evidence regarding co-morbid Th2 mediated diseases will be reviewed here-in.

Asthma and EOE

Asthma and EOE are frequently associated, and some have suggested that EOE may be the asthma of the esophagus. Asthma and EOE share many commonalities in that they are both chronic immune mediated conditions, characterized by inflammatory changes within the mucosa and submucosa with a predominant eosinophil infiltrate.[23] While the relationship between asthma and EOE remains poorly understood, several database studies have sought to determine the prevalence of co-existent asthma and EOE.[24] Within the United States, EOE patients were found to have co-morbid asthma 23.4–37.5% of the time.[25–27] The two diseases were found to co-exist more frequently in the pediatric population.[27] Other retrospective studies throughout the world have been less clear-cut, reporting that between 12–68% of patients with EOE have a history of asthma.[24] Furthermore, a recent systematic review and meta-analysis by Gonzalez-Cervera et al[28] found that bronchial asthma is significantly more common among EOE patients of all ages when compared to controls,

with an overall odds ratio (OR) of 3.01 (95% CI 1.96–4.62). Similar ORs were found when comparing adults and children separately.

Asthma and AD

The concept of the "atopic march" has been investigated for decades, following clinical observations of co-morbid disease states such as food allergy, allergic rhinitis, and asthma progressing from atopic dermatitis. Although the interplay between AD and asthma continues to be investigated, impaired skin barrier function has been suggested as an entry point for allergen penetration and the further development of atopic disease.[29] Additionally, it has since been shown that the presence of atopic dermatitis in children significantly increases the likelihood asthma development.[30] Several large database studies out of the US have investigated the prevalence of co-morbid asthma in AD patients. Silverberg and Simpson[31] utilized the 2007 National Survey of Children's Health and found the lifetime and 1-year prevalence of self reported asthma to be 25.1% and 19.8%, respectively. Data from the 2012 National Health Interview Survey reported similar numbers from an adult US population (25.5% and 18.7% for lifetime and 1-year prevalences).[32] More recently, a 2018 study reported a 49.8% prevalence of comorbid asthma in AD patients, and calculated a relative risk of 1.73 (95% CI 1.53–1.93).[33]

Asthma and CRS

While CRS is broadly categorized into two predominant phenotypes [CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP)], recent developments of CRS endotypes have allowed for better understanding of the pathogenesis of disease. CRSwNP patients with Th2 endotypes often have severe disease that is difficult to manage and frequently have comorbid lower airway disease.[34] Interestingly, similar inflammatory profiles have been found in nasal polyp specimens and bronchial specimens in CRSwNP patients, indicating the existence of similar inflammation throughout the upper and lower airways in these patients.[35] Surprisingly, however, Th2 cytokine concentrations were significantly higher in nasal polyps compared to bronchial specimens, leading the authors to question whether the sinus disease plays an important role in lower airway inflammation.[35] Several, large studies have consistently associated asthma with CRSwNP and vice-versa. Results from the Global Allergy and Asthma Network of Excellence, multicenter, population-based

survey identified strong, consistent correlations between asthma and CRS among all centers, and calculated an overall OR of 3.48 (95% CI 3.21–3.77). Among patients with CRS, some studies have suggested a 60% prevalence of comorbid lower airway disease.[36] Additionally, asthma patients with comorbid CRS have been shown to have higher levels of lower airway inflammation and worse asthma control than those without CRS.[37,38]

EOE and AD

Although it is the most recently recognized clinical entity of the disease discussed in this manuscript, EOE research has focused on identifying frequently associated comorbid conditions in an attempt to better understand the disease process. Recent studies in the EOE literature have reported prevalence rates of AD between 7%-55% amongst EOE patients.[39–42] Additionally, a recent systematic review and meta-analysis compared the frequency of atopic dermatitis between EOE patients and control subjects.[28] The authors reported a pooled OR of 2.85 (95% CI: 1.87–4.34), with no significant difference noted when performing subgroup analysis including adult and pediatric patients separately. Genetic analyses have also identified common predisposing factors to EOE and AD, as polymorphisms in thymic stromal lymphopoietin and loss of function mutations in filaggrin, an epithelial differentiation gene, have been shown to increase the risk of both EOE and AD.[43] Additionally, recent transcriptome analysis has suggested similar disease mechanisms between EOE and AD.[43]

EOE and CRS

Until 2016, no studies had specifically investigated the coexistence of EOE and CRS. Utilizing a large genealogical database, however, Padia et al[44] were able to investigate this particular association. Amongst patients with CRS, the authors reported a 3.44 times increased risk of having EOE. This risk extended to first degree relatives of the CRS proband (OR 1.45; 95% CI: 1.23–1.71), regardless of whether the relative also carried a CRS diagnosis.[44] Reverse comparison starting with EOE patients found that probands with EOE were 2.86 times more likely to have CRS than matched controls. Again, this increased risk was carried to EOE patients first degree relatives with OR 1.48 (95% CI: 1.25–1.76).[44]

AD and CRS

Despite having less studies investigating the prevalence of comorbid AD and CRS, a few studies have provided supporting data. In a large, retrospective longitudinal cohort study, Tan et al[45] identified an association between a pre-morbid diagnosis of AD and the subsequent development of CRS. Similarly, Chandra et al[46] reported a significantly increased prevalence of CRSwNP in patients with AD compared with a control population with hypertension. In another study, a reverse comparison was performed and demonstrated that patients with CRS were at a greater risk of developing AD compared to a control population, with a hazard ratio of 2.75 (95% CI: 1.23–6.16).[47]

Impact of Treatment of Comorbid Type 2 Inflammatory Diseases

As more is discovered about the impact of comorbid inflammatory diseases, researchers will be motivated to investigate how the treatment of comorbid conditions affects patient outcomes.

Although robust studies investigating the effects of concomitant asthma and EOE on disease outcomes are lacking, smaller studies have reported interesting findings. Rajan et al[48] found that patients with both EOE and asthma had higher baseline tissue eosinophils than non-asthmatics. Additionally, despite other inflammatory parameters being similar, EOE asthmatics had a higher rate of non-response to anti-inflammatories compared to non-asthmatics. Another retrospective review of asthma patients concluded that the use of inhaled corticosteroids appears to be protective against EOE, speculating that control of the airway disease may be therapeutic in treating EOE, although it is difficult to make such speculations with a single retrospective study.[49]

Similarly, the implications of comorbid asthma and CRS have been thoroughly investigated. In studies, severe asthmatics with associated CRSwNP require more frequent oral corticosteroid usage when compared to asthmatics without CRS.[50] Several other studies have suggested that treatment of CRS may optimize asthma control. Zhang et al[51] demonstrated greater quality of life improvement in comorbid CRSwNP and asthma patients after endoscopic sinus surgery compared CRS patients without asthma or polyps. Additionally, Schlosser et al[52] reported improved asthma control and asthma-related quality of life following sinus surgery. Despite these findings, it has also been reported that comorbid asthma and CRSwNP are more likely to require a greater number of sinus surgeries than patients with CRSwNP alone.[53]

The recent introduction of biologics targeting Th2 inflammation will certainly have an impact on the treatment of comorbid inflammatory diseases (Table 1). Studies have already shown promising results with the addition of biologics, with one study demonstrating a 50% reduction in outpatient office visits for atopic disease and CRS in patients with severe asthma after starting mepolizumab, an anti-IL-5 biologic.[54] Omalizumab, an anti-IgE monoclonal antibody is

Table 1 Biologics in Type 2 Inflammatory Diseases

Biologic	Target	Indications	Evidence
Omalizumab	IgE	Asthma CRSwNP CIU	**Asthma**: Reduced exacerbations; Potentially improved asthma control; QOL improvement; Possible low increased risk of AE[58]
			EOE: Two clinical trials with conflicting data on histological and symptom improvement.[59,60] Placebo controlled study found no difference.
			AD: Inconclusive results from 3 small RCTs. Strong placebo responses when measuring clinical outcomes may have affected outcomes.[61–63]
			CRS: 2 RCTs demonstrated objective improvement in polyp scores and imaging. Conflicting data regarding quality of life.[64,65] 2 recently completed large RCTs showed improved QOL and endoscopic appearance of the sinus cavities.[66]
Mepolizumab	IL-5	Asthma	**Asthma**: Reduced exacerbations; Potentially improved asthma control; QOL improvement; reduced daily OCS use; improved lung function; increased likelihood of drug-related AE.[58]
			EOE: Reduces esophageal eosinophil counts in adults and children; symptom/QOL improvement is inconclusive.[11,13]
			AD: A single clinical trial was terminated early due to interim analysis meeting pre-specified futility criteria.[67]
			CRS: Improvement in nasal polyp scores; symptom reduction; reduced need for surgery.[68,69]
Reslizumab	IL-5	Asthma	**Asthma**: Reduced exacerbations; Improved QOL; Improved lung function; Probable increased risk of drug related AE[58]
			EOE: Reduces esophageal eosinophil counts; No improvement in esophageal symptoms.[12]
			AD: Limited data; No active clinical trials.
			CRS: Reduction in nasal polyp score and blood eosinophil counts; no investigation on symptom scores.[70]
Benralizumab	IL-5R	Asthma	**Asthma**: Reduced exacerbations; Improved QOL; Reduced daily OCS use; Improved lung function; Probable increased risk of drug related AE[58]
			EOE: Limited data; Phase 3 clinical trial is currently enrolling patients.[71]
			AD: Limited data; Phase 2 clinical trial is currently enrolling patients.[72]
			CRS: Preliminary data demonstrated safety;[73] current Phase 3 trial evaluating efficacy currently enrolling.[74]
Dupilumab	IL-4/-13	Asthma Atopic Dermatitis CRSwNP	**Asthma**: Reduced exacerbations; Potentially improved asthma control; QOL improvement; reduced daily OCS use; improved lung function; possible low risk of increased AE.[58]
			EOE: Reduces esophageal eosinophil counts; Improves endoscopy scoring; QOL improvement.[14]
			AD: Significantly improves patient reported QOL metrics; reduced need for rescue medication.[75]
			CRS: Reduces nasal polyp scores; reduces Lund-Mackay scores; improves SNOT-22 scores.[22]

Note: Bold text in the "Evidence" column designates the disease state for which the following evidence is attributed to.
Abbreviations: IgE, Immunoglobulin E; IL, Interleukin; IL-5R, Interleukin 5 receptor; CIU, chronic idiopathic urticaria; EOE, Eosinophilic esophagitis; AD, atopic dermatitis; CRS, chronic rhinosinusitis; QOL, quality of life; AE, adverse event; RCT, randomized controlled trial; OCS, oral corticosteroid; SNOT-22, sinonasal outcome test-22.

currently approved in the US for the treatment of asthma and CRSwNP. Studies investigating the utility of omalizumab in AD have been inconclusive.[55] Additionally, dupilumab, which targets the shared receptor subunit for IL-4 and IL-13, has shown good results in the treatment of asthma, AD, and CRS.[56] A recent Phase 2 clinical trial has also shown promise in the management of EOE,[14] results that other biologic agents have failed to produce up to this point.[57] So, while it is clear that we have made great strides over the past few decades in the treatment of Th2 mediated diseases, questions still remain and further research must be conducted to better understand the epidemiological variability across these disease states.

Disclosure

Dr Jivianne Lee reports personal fees from Sanofi and Regeneron, outside the submitted work. The authors report no other potential conflicts of interest for this work.

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