Clinical Commentary Review

The Unified Airway Hypothesis: Evidence From Specific Intervention With Anti–IL-5 Biologic Therapy

Claus Bachert, MD, PhD[a,b,c,d], Amber U. Luong, MD, PhD[e], Philippe Gevaert, MD, PhD[d], Joaquim Mullol, MD, PhD[f], Steven G. Smith, PhD[g], Jared Silver, MD, PhD[h], Ana R. Sousa, PhD[i], Peter H. Howarth, MD, DM[j,k], Victoria S. Benson, PhD[l], Bhabita Mayer, MSc[m], Robert H. Chan, MD[i], and William W. Busse, MD[n] *Muenster, Germany; Stockholm, Sweden; Guangzhou, China; Ghent, Belgium; Houston, Texas; Barcelona, Catalonia, Spain; Durham, NC; Brentford and Southampton, United Kingdom; and Madison, Wis*

The unified airway hypothesis proposes that upper and lower airway diseases reflect a single pathological process manifesting in different locations within the airway. Functional, epidemiological, and pathological evidence has supported this well-established hypothesis for some time. However, literature on the pathobiologic roles/therapeutic targeting of eosinophils and IL-5 in upper and lower airway diseases (including asthma, chronic rhinosinusitis with nasal polyps [CRSwNP], and nonsteroidal anti-inflammatory drug-exacerbated respiratory disease) has recently emerged. This narrative review revisits the unified airway hypothesis by searching the scientific literature for recent learnings and clinical trial/real-world data that provide a novel perspective on its relevance for clinicians. According to the available literature, eosinophils and IL-5 have important pathophysiological roles in both the upper and lower airways, although the impact of eosinophils and IL-5 may vary in asthma and CRSwNP. Some differential effects of anti–IL-5 and anti–IL-5-receptor therapies in CRSwNP have been observed, requiring further investigation. However, pharmaceutical targeting of eosinophils and IL-5 in patients with upper, lower, and comorbid upper and lower airway inflammation has led to clinical benefit, supporting the hypothesis that these are linked conditions manifesting in different locations. Consideration of this approach may improve patient care and aid clinical decision making. **(J Allergy Clin Immunol Pract 2023;11:2630-41)**

Key words: *Unified airway; Eosinophils; IL-5; Asthma; Chronic rhinosinusitis with nasal polyps; Nonsteroidal anti-inflammatory drug-exacerbated respiratory disease*

[a]Department of Otorhinolaryngology, Head and Neck Surgery, University of Muenster, Muenster, Germany
[b]Department of Ear, Nose and Throat Diseases, Karolinska University Hospital, Stockholm, Sweden
[c]Department of Otorhinolaryngology, The First Affiliated Hospital of Sun Yat-sen University, Sun Yat-sen University, Guangzhou, China
[d]Upper Airway Research Laboratory, Ghent University Hospital, Ghent, Belgium
[e]McGovern Medical School of the University of Texas Health Science Center, Houston, Texas
[f]Department of Otorhinolaryngology, Hospital Clínic, IDIBAPS, Universitat de Barcelona, CIBERES, Barcelona, Catalonia, Spain
[g]Respiratory Therapeutic Area Unit, GSK, Durham, NC
[h]US Medical Affairs - Respiratory, GSK, Durham, NC
[i]Clinical Sciences - Respiratory, GSK, Brentford, United Kingdom
[j]Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton and NIHR Respiratory Biomedical Research Unit, Southampton General Hospital, Southampton, United Kingdom
[k]Global Respiratory Franchise, GSK, Brentford, United Kingdom
[l]Epidemiology, Value Evidence and Outcomes, GSK, Brentford, United Kingdom
[m]Clinical Statistics, GSK, Brentford, United Kingdom
[n]Division of Allergy, Pulmonary and Critical Care Medicine, Department of Medicine, University of Wisconsin, Madison, Wis

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Corresponding author: Claus Bachert, MD, PhD, Department of Otorhinolaryngology, Head and Neck Surgery, University of Muenster, Kardinal-Von-Galen-Ring 10, Muenster 48149, Germany. E-mail: claus.bachert@ukmuenster.de.
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Abbreviations used
CRSwNP- chronic rhinosinusitis with nasal polyps
IL-5R- IL-5 receptor
NSAID-ERD- nonsteroidal anti-inflammatory drug-exacerbated respiratory disease
OCS- oral corticosteroid
QOL- quality of life
SCS- systemic corticosteroid

INTRODUCTION

The unified airway hypothesis is an established concept that the upper and lower airways form a single unified organ that is interconnected and interrelated by several physiologically important shared traits.[1-3] These shared traits include immunology and pathophysiology, epidemiology, and clinical characteristics.[4,5] The main basis of the unified airway hypothesis is that diseases of the upper and lower airways frequently occur together, and may reflect a single pathologic process manifesting in different locations within the airway.

There are several lines of evidence that substantiate the unified airway hypothesis (Figure 1).[4,5,6] First, the upper and lower airways share functional and histological similarities; the sinuses and upper airways are structurally connected to the lower airways via the larynx and share several common cell and tissue types, including ciliated epithelium, glands and goblet cells, basement membrane, and lamina propria.[7] Second, epidemiological evidence demonstrates that countries with a high prevalence of upper airway disease also have a high prevalence of lower airway disease.[8] Accordingly, asthma and chronic rhinosinusitis with nasal polyps (CRSwNP) are commonly comorbid conditions, occurring together in 20% to 70% of patients (Figure 1).[9,10-12] Moreover, nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (NSAID-ERD) is characterized by chronic persistent asthma and CRSwNP (which are exacerbated by nonsteroidal anti-inflammatory drugs)[13] and occurs in up to 10% of patients with CRSwNP and 15% of patients with severe asthma.[14] Patients with comorbid upper and lower airway disease also tend to have the poorest disease outcomes; for example, patients with comorbid asthma and CRSwNP have more difficult-to-treat asthma/CRSwNP symptoms, are more prone to asthma exacerbations, and have higher rates of nasal polyp recurrence and corticosteroid dependence than those without.[9] Furthermore, patients with NSAID-ERD have a more significantly impaired sense of smell and require more sinus surgeries, compared with those who have CRSwNP alone.[15,16]

Finally, chronic inflammatory diseases of the upper and lower airways present in several phenotypes (observable clinical characteristics or traits of a disease) and shared endotypes (subtypes of a disease that are defined by distinct pathophysiologic mechanisms). Endotypes of upper and lower airway disease include type 1 (driven by IFN-γ, IL-2, and lymphotoxin-α responses[24]), type 2 (mediated by the cytokines IL-4, IL-13, and IL-5 and immune cells such as eosinophils and mast cells[17,24]), and type 3 (associated with neutrophilia and driven by T_H17 cells, IL-6, and IL-17[25,26]) inflammatory endotypes. CRSwNP and severe eosinophilic asthma (severe phenotypes of chronic rhinusinusitis and asthma) and NSAID-ERD can present with any 1 or a combination of these inflammatory endotypes,[27-30] but are frequently associated with type 2 inflammation including elevated tissue and serum eosinophil counts alongside elevated levels of IL-5, IL-4, and IL-13.[27,28,30] Although the pathophysiologic roles of type 2 inflammatory factors in asthma are well known, their exact roles in CRS with and without NP are comparatively poorly understood.[31,32]

Despite their similarities, the upper and lower airways contain unique organs with variations in tissue and cell types. For example, the organs of the upper versus lower respiratory tract have unique physiological functions, with the upper respiratory tract serving to humidify, warm, and filter air while the lower respiratory tract is involved in gas exchange.[33] In terms of differences in cell type, although the upper and lower respiratory tract is mostly lined by respiratory epithelium (pseudostratified columnar ciliated epithelium), the bronchioles are lined by simple columnar and cuboidal epithelium and the alveoli are lined by thin squamous epithelium to permit gas exchange.[33] Physiologically, reversible airflow obstruction has distinct mechanisms at the 2 sites and is related to vascular engorgement in the upper airways and smooth muscle constriction within the lower airways, with differing influences of type 2 inflammatory mediators on these processes.[34,35] Diseases of the upper versus lower respiratory tract thus have differences in their presentation, diagnosis, and management, as reflected by current clinical recommendations.[18,36,37] Accordingly, the upper and lower airways are sometimes considered clinically separate (though comorbid) entities, with different health care specialists treating upper versus lower respiratory organs.

Although the unified airway hypothesis was established some time ago, an emerging body of literature on the pathophysiology and treatment of upper and lower airway diseases has since become available.[19] Randomized controlled trials assessing the efficacy of biologic therapies for the treatment of upper and lower airway diseases provide a rich source of data, which may support and further substantiate the merits of the unified airway hypothesis. For example, biologic trials in patients with CRSwNP often assess some asthma-related efficacy outcomes and vice versa. The current literature lacks scrutiny of how these biologic efficacy data might support the clinical and scientific relevance of the unified airway hypothesis, in addition to improving clinical understanding of this concept. This narrative review will revisit the unified airway hypothesis focusing on the shared endotype of elevated eosinophils and IL-5 in clinically severe asthma, CRSwNP, and NSAID-ERD. An in-depth examination of data from clinical trials and real-world studies rooted in IL-5 inhibition will further illustrate and help validate this hypothesis. Ultimately, this review will aim to provide a novel perspective and update the relevance of the unified airway hypothesis for clinical practice and health care practitioners.

EOSINOPHILS, IL-5, AND THE UNIFIED AIRWAY HYPOTHESIS

Eosinophils are immune effector cells that have important roles in mucosal defense and mediating type 2 inflammation under normal physiological conditions; they are also thought to be involved in maintaining homeostasis in several organs.[31,32] IL-5 is the major cytokine responsible for the proliferation, activation, and survival of eosinophils,[38] although its effects are increasingly understood to extend beyond eosinophil biology.[32,39-41] Elevated levels of eosinophils and IL-5 in the peripheral blood and/or tissues are observed in several type 2 inflammatory conditions such as severe eosinophilic asthma,

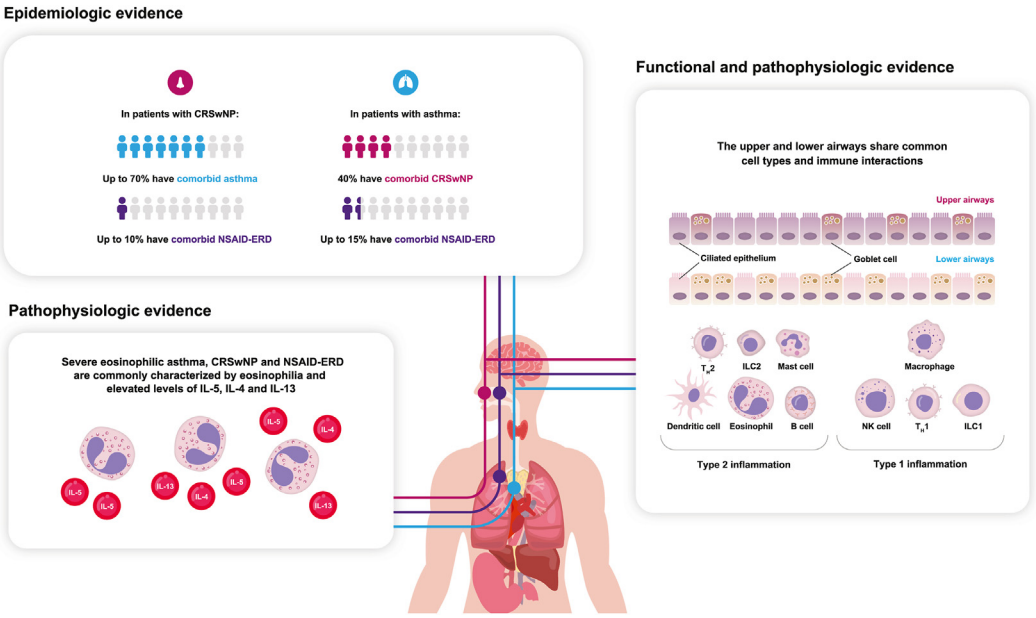

FIGURE 1. Functional,[7,17] epidemiologic,[2,9,14,18-21] and pathophysiologic[21-23] evidence for the unified airway hypothesis. *ILC*, Innate lymphoid cell; *NK*, natural killer.

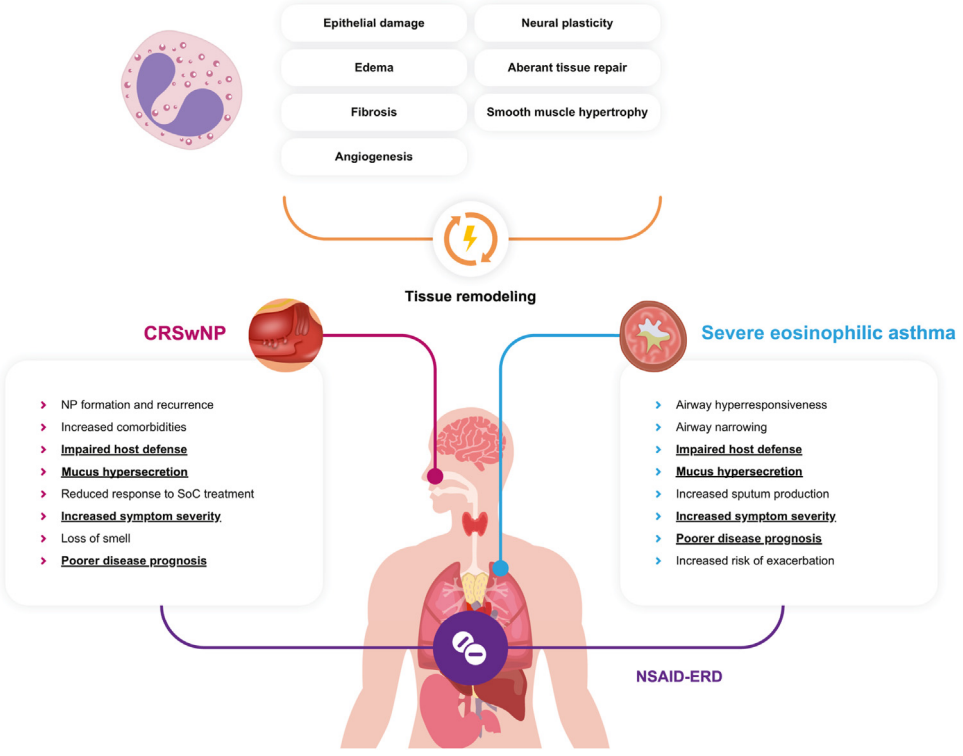

FIGURE 2. The roles of eosinophils in tissue remodeling in diseases of the unified airway, including severe eosinophilic asthma, CRSwNP, and NSAID-ERD.[17,31,32,47-51] Clinical implications of tissue remodeling common to severe eosinophilic asthma and CRSwNP are underlined. *SoC*, Standard of care.

CRSwNP, eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndromes, and chronic obstructive pulmonary disease.[42] Eosinophils have been implicated in several processes including epithelial damage, smooth muscle hypertrophy, angiogenesis, neural plasticity, and aberrant tissue repair, all of which promote pathological tissue remodeling (Figure 2).[31,32]

In patients with asthma, airway mucus plugging (an important consequence of eosinophilic airway inflammation) can lead to airflow obstruction.[43] The association between eosinophilic inflammation and mucus plugging is supported by a correlation between elevated sputum eosinophils and greater airway mucus plugging on computed tomography scan in patients with asthma[44]; the presence of eosinophil peroxidase altering the property of mucus to make it more viscous/difficult to expectorate[43]; and local eosinophilic inflammation leading to impaired mucociliary clearance.[45] Furthermore, eosinophils are a major source of IL-13, a stimulator of mucus generation in asthmatic airways.[46] The pathological processes linked to eosinophilic inflammation and airway remodeling also underlie increased exacerbation risk and symptom severity in patients with asthma.[17,47,48] Although tissue remodeling in CRSwNP is less well understood, elevated eosinophil levels are believed to increase symptom severity and mucus production, and result in NP recurrence while negatively impacting disease prognosis and response to treatment.[49,50]

Eosinophils and the inflammatory mediators they secrete have the potential to cause several key clinical features of asthma and CRSwNP. When activated, eosinophils release a plethora of inflammatory mediators, including granule proteins, enzymes, cytokines, chemokines, growth factors, lipids, and oxidative products.[32] Some of these inflammatory mediators are upregulated in patients with severe eosinophilic asthma and with CRSwNP[52-57] and have potential pathologic roles in these diseases beyond maintaining chronic inflammation. For example, major basic protein is toxic to respiratory epithelium, eosinophil cationic protein alters the permeability of cell membranes, and eosinophil-derived neurotoxin is damaging to neurons.[58] These proteins are therefore likely to contribute to damage of the epithelial barrier and subsequent tissue remodeling observed in patients with asthma and CRSwNP[59-61]; based on their functional properties, eosinophil cationic protein and eosinophil-derived neurotoxin may also be responsible for disrupted olfaction in CRSwNP.[32] Moreover, eosinophils secrete cysteinyl leukotrienes that cause bronchoconstriction and altered vascular permeability in asthma,[62] in addition to potentially promoting edema and nasal congestion in CRSwNP and increasing disease severity in NSAID-ERD.[63,64] Eosinophils also release extracellular DNA traps (eosinophilic extracellular traps) and Charcot-Leyden crystals/galectin-10 on activation, often in response to microbial infection or allergic inflammation.[32,65] Among patients with asthma, extracellular eosinophilic traps contribute to airway epithelial damage and negatively correlate with lung function.[66,67] In addition, Charcot-Leyden crystals/galectin-10 may contribute to mucus production and the tenacity of mucus plug formation, as well as being a biomarker for eosinophilic airway inflammation.[68-70] In CRSwNP, both extracellular eosinophilic traps and Charcot-Leyden crystals are strongly associated with disease severity and may negatively impact olfaction.[32] Finally, IL-5 may downregulate epithelial tight junction protein expression,[39] and therefore may increase epithelial susceptibility to eosinophil-directed damage and subsequent fibrosis and thickening of the basement membrane (as a result of the epithelial-mesenchymal signaling) during the repair response process.[60] This indirect stimulation of myofibroblast transformation and enhanced collagen synthesis will be complemented by the direct activation of fibroblasts by IL-5.[71] Locally produced IL-5 may also prolong eosinophil survival,[72] thus facilitating eosinophil accumulation in the airways and nasal mucosa of patients with asthma and CRSwNP, respectively.

Beyond eosinophils, several other immune cells that secrete IL-5 and/or express the IL-5 receptor (IL-5R) are elevated in the respiratory tissues of patients with asthma and/or CRSwNP,[40,73] indicating a potential eosinophil-independent role of IL-5 in the pathobiology of both diseases (Figure 3).[32,39,40,71,72,74-89] These include mast cells, basophils, type 2 innate lymphoid cells, and plasma cells; interactions between IL-5 and these cells have been described throughout the literature.[32,39,40,72,74-82] In addition, human airway neutrophils recovered by human bronchoalveolar lavage fluid have been reported to express IL-5 receptors capable of signal transduction[75] and human airway epithelial cells and lung fibroblasts are also recognized to express functional IL-5R.[39,71]

Clinically, although severe asthma and CRSwNP are both predominantly eosinophilic conditions,[22,90] the role of eosinophils in driving the severity of each disease can vary.[91] Although definitions of eosinophilia are highly variable across the available literature, the proportions of patients with asthma (of any phenotype/endotype) and with CRSwNP who have elevated blood or tissue eosinophils range from approximately 40% to 42%[92-94] and 46% to 66%, respectively, at any 1 cross-sectional time point.[95-100] However, over a 10-year observation period, more than 80% of patients with severe asthma have blood eosinophil counts of at least 300 cells/μL at some time point.[101] Peripheral blood eosinophils are consistently considered a robust and reliable biomarker for the diagnosis and monitoring of severe eosinophilic asthma.[37,102,103] In this asthma population, elevated blood eosinophil counts are associated with worse asthma control and an increased risk of severe exacerbations.[104,105] Furthermore, higher blood eosinophil counts predict increased disease burden, health care resource utilization, and costs for these patients.[106,107] In patients with CRSwNP, the utility of blood and tissue eosinophil counts for the diagnosis and monitoring of CRSwNP is less clear. However, some recent studies have associated elevated blood and/or tissue eosinophil counts with increased disease severity and NP recurrence, impaired olfaction, and a higher need for repeat sinonasal surgery in patients with CRSwNP[36,108-111] (however, it should be noted that not all studies have found such associations).[99,112,113] Elevated tissue IL-5 has also been demonstrated to predict NP recurrence in patients with CRSwNP.[114] Interestingly, studies have shown that the highest blood eosinophil counts and/or NP tissue eosinophils are observed in patients with comorbid upper and lower airway disease (vs those with severe eosinophilic asthma or CRSwNP alone),[113,115-117] consistent with increased systemic IL-5 signaling to the bone marrow in patients with type 2 upper and lower airway disease.[118] Furthermore, in a study of patients with CRSwNP, the postsurgical recurrence of NP was higher among patients with comorbid asthma than among those without.[117] Indeed, the presence of comorbid eosinophilic asthma substantially increases the probability that a patient's nasal polyps will be eosinophilic.[119] One interesting potential exception can be found in patients with allergic fungal rhinosinusitis, who have high levels of eosinophils within the inflamed sinus mucosa despite having generally normal blood eosinophil counts.[120] Moreover, although the prevalence of comorbid asthma is higher among patients with allergic fungal rhinosinusitis than among those with CRS and no NP, it is much lower than the prevalence of asthma among patients with a diagnosis of CRSwNP.[121] This suggests a potential link specifically between

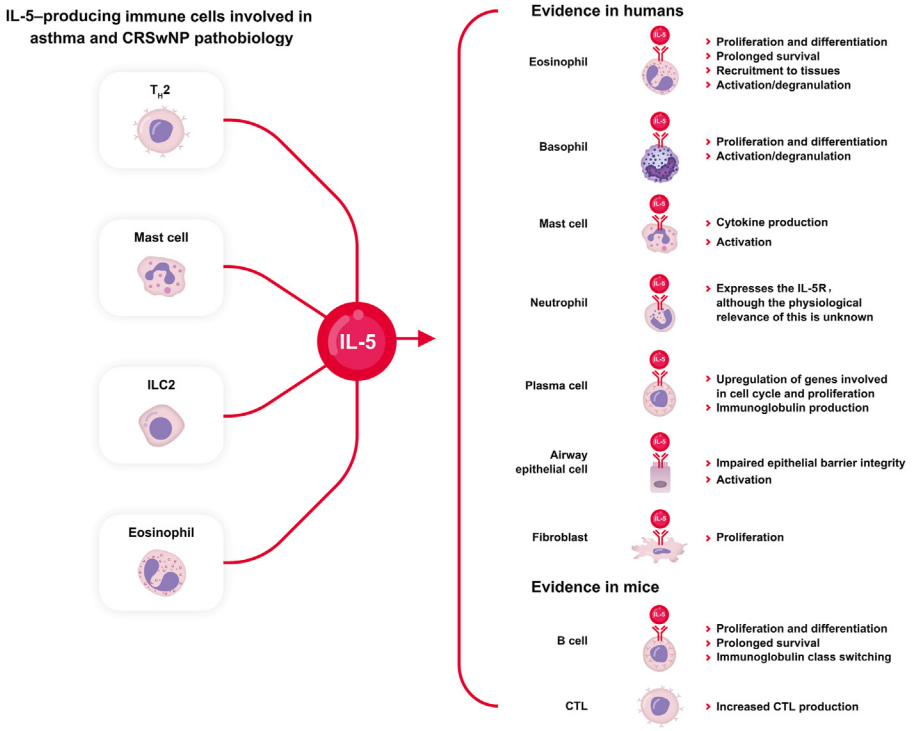

FIGURE 3. Evidence for the effects of IL-5 signaling in different cell types.[32,39,40,71,72,74-88] Evidence in humans includes a combination of *in vitro*, *ex vivo*, and *in vivo/in situ* data. *CTL*, Cytotoxic T lymphocyte; *ILC2*, innate lymphoid cell type 2.

elevated blood eosinophils and comorbid upper and lower airway disease, although further research is needed to substantiate this. Taken together, these findings indicate that eosinophils and IL-5 play a crucial role in the pathophysiology of asthma and CRSwNP, and although deeper insight into the noneosinophilic effects of IL-5 are needed, their presence and known functions in both diseases support a therapeutic approach that treats the upper and lower airways as a single unit.

CLINICAL BENEFITS OF STANDARD-OF-CARE THERAPY DEMONSTRATE UPPER AND LOWER AIRWAY INTEGRATION

Inhaled and systemic corticosteroids are known to reduce eosinophilic inflammation and are standard-of-care treatment for severe eosinophilic asthma.[122] In addition to improving asthma outcomes in patients with severe eosinophilic asthma, short-term systemic corticosteroids (SCSs) can reduce nasal polyp size in CRSwNP.[123] As previously mentioned, patients with comorbid upper and lower airway disease have higher corticosteroid dependence than those without.[9] In a study in patients with a primary diagnosis of CRSwNP, those with comorbid late-onset asthma had significantly higher use of nasal steroid sprays and oral corticosteroids (OCSs) for the treatment of NP.[124] Studies assessing the potential differential efficacy of SCSs in patients with versus without comorbid upper and lower airway disease are limited.[125] However, in 2 studies of patients with CRSwNP, the level of sinonasal clinical benefit experienced with OCS treatment was not influenced by the presence/absence of comorbid asthma.[126,127] Conversely, in another study, patients with CRSwNP and comorbid asthma were less likely to experience post-OCS improvements in QOL (measured by the 22-item SinoNasal Outcomes Test total score) than those without.[128] Overall, these studies indicate that although the presence of comorbid upper and lower airway disease can lead to higher primary disease severity and a higher need for OCSs (thus supporting the unified airway hypothesis), the impact of treating concomitant upper and lower airway manifestations with OCSs can be variable, and may depend on whether the disease is inflammatory or remodeled.[11,129,130]

For patients with CRSwNP who do not respond to pharmaceutical standard- of-care interventions, endoscopic sinus surgery to remove the NP tissue is an option. Patients with CRSwNP and comorbid asthma or NSAID-ERD undergo more sinonasal surgeries than do those with CRSwNP alone.[9] In 11 studies following patients with comorbid asthma for 6 to 120 months after endoscopic sinus surgery (with most [9 of 11] followed for 12 months), the need for OCSs for asthma control decreased in 73% of patients.[129] Several other studies have noted reductions in asthma exacerbations and improvements in asthma symptoms and control following endoscopic sinus surgery.[129-131] Although these were unblinded and uncontrolled studies, overall they suggest that clinical benefits to the lower airways (including improved asthma control) can occur following the surgical removal of upper airway nasal polyp tissue, thus indicating that upper and lower airway diseases can be treated as manifestations of a common pathology.

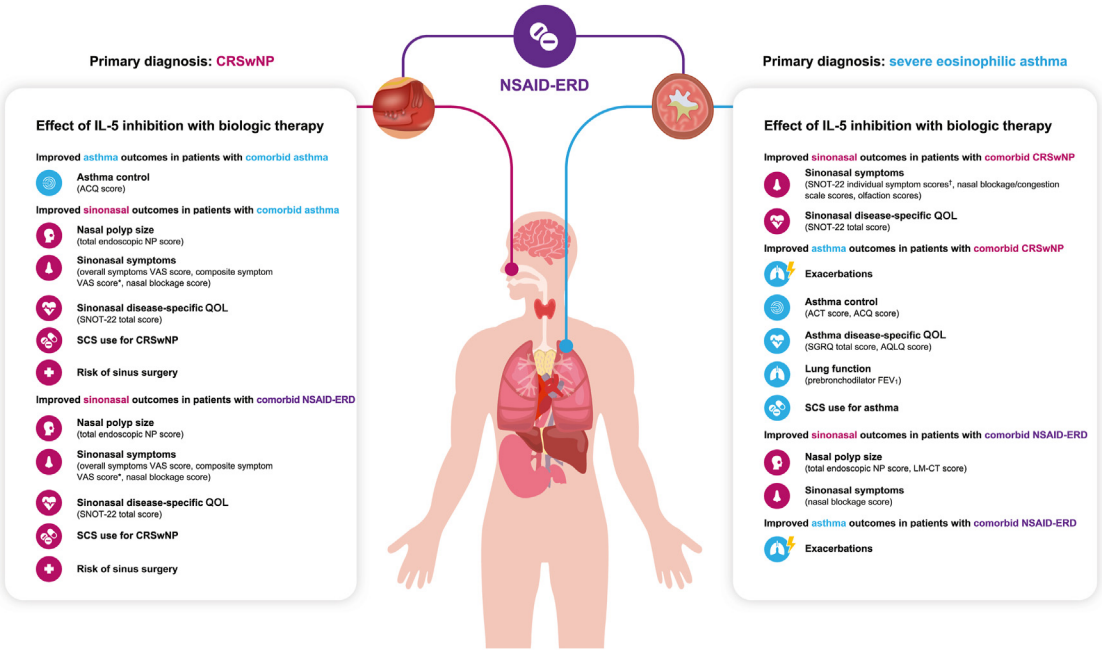

FIGURE 4. Clinical evidence for the unified airway hypothesis: benefits of anti—IL-5— targeted biologics demonstrate upper and lower airway integration.[115,116,132,142-156] Some (but not all) of the analyses summarized here compared asthma/CRSwNP/NSAID-ERD comorbidity subgroups against controls without the comorbidity of interest and either found clinical improvement irrespective of the presence/absence of comorbidity or larger clinical improvements in patients with vs without comorbid asthma/CRSwNP/NSAID-ERD. Please refer to the main text for further details. *ACQ*, Asthma control questionnaire; *ACT*, asthma control test; *AQLQ*, asthma quality of life questionnaire; *LM-CT*, Lund-McKay computer tomography; *NP*, nasal polyp; *NPS*, nasal polyp score; *SGRQ*, St George's Respiratory Questionnaire; *SNOT-22*, 22-item sinonasal outcomes test; *VAS*, visual analogue scale. *Composite symptom VAS score combined patients' individual scores for nasal obstruction, nasal discharge, mucus in throat, and loss of smell. †SNOT-22 individual symptom scores included nasal obstruction, nasal discharge, loss of smell, facial pain, and ear fullness.

CLINICAL BENEFITS OF BIOLOGIC THERAPY DEMONSTRATE UPPER AND LOWER AIRWAY INTEGRATION

Owing to similarities in the inflammation that underlies the upper and lower airways, several anti-inflammatory biologic therapies have been associated with clinical benefits in both upper and lower airway disease. Among the mAb therapies that do not target IL-5 or the IL-5R,[19] omalizumab (anti-IgE) and dupilumab (anti—IL-4/13) improve asthma outcomes in patients with a primary diagnosis of asthma and improve sinonasal outcomes in patients with a primary diagnosis of CRSwNP, compared with placebo.[132-136] Of note, the dupilumab-associated clinical improvements in patients with asthma or CRSwNP were more pronounced in patients with comorbid upper and lower airway disease than in those without.[137-139]

Biologics that target IL-5 or the IL-5R include mepolizumab (anti—IL-5, approved for the treatment of both severe eosinophilic asthma and severe CRSwNP, among other eosinophilic diseases), reslizumab (anti—IL-5, approved for the treatment of severe eosinophilic asthma), and benralizumab (anti—IL-5R, approved for the treatment of severe eosinophilic asthma).[31,140,141] Evidence from numerous phase IIb and III trials for these biologics has shown that anti—IL-5/IL-5R therapy is efficacious across various clinically relevant end points in patients with severe eosinophilic asthma and CRSwNP.[140] Many of the patients enrolled in these trials and in subsequent real-world studies had comorbid CRSwNP or NSAID-ERD, allowing for some insightful *post hoc* and real-world analyses on the clinical impact of these treatments among patients with both upper and lower airway manifestations. These are summarized in Figure 4[115,116,132,142-156] and described in more detail below.

A combination of clinical trial and real-world data on mepolizumab shows that in patients with severe eosinophilic asthma, those with comorbid CRSwNP also experience improvements in their sinonasal outcomes in response to IL-5 inhibition versus placebo (Figure 4).[115,116,132,142-156] These outcomes include improvements in sinonasal disease-specific quality of life (QOL),[137,138] sinonasal symptoms,[150,151] and nasal polyp size (Figure 4).[149,151] As expected, improvements in sinonasal disease-specific QOL were larger in patients with comorbid CRSwNP than in those without CRSwNP.[148] Treatment with benralizumab (anti—IL-5R) results in similar clinical benefits in the upper airways of patients with a primary diagnosis of severe eosinophilic asthma, as evidenced by posttreatment improvements in sinonasal disease-specific QOL,[115,143,152-155,157] nasal polyp size,[152,155] sinonasal symptoms,[152] and olfaction.[115]

Interestingly, clinical trials and real-world studies of anti—IL-5/5R biologics in patients with severe eosinophilic asthma have shown improvements versus placebo or no biologic treatment in

asthma outcomes (including exacerbation rates, lung function, asthma control, asthma disease-specific QOL, and corticosteroid dependence) among patients with comorbid upper and lower airway disease, which were sometimes larger than the overall study populations (Figure 4).[116,142,144,145,153,158,159] Furthermore, in some of these studies, the improvements in asthma outcomes were significantly greater in patients with versus without comorbid CRSwNP.[144,145,153] In an unpublished *post hoc* meta-analysis of 2 phase III mepolizumab trials (GSK-funded; Efficacy and Safety Study of Mepolizumab Adjunctive Therapy in Subjects With Severe Uncontrolled Refractory Asthma [MENSA; NCT01691521] and Efficacy and Safety Study of Mepolizumab Adjunctive Therapy in Participants With Severe Eosinophilic Asthma on Markers of Asthma Control [MUSCA; NCT02281318]) including only the approved dose of mepolizumab 100 mg subcutaneously, improvements in the 5-item asthma control questionnaire were larger among patients with versus without comorbid CRSwNP (inverse variance-weighted fixed-effects meta-analysis: treatment difference, mepolizumab-placebo [95% CI], −0.69 [−1.02 to −0.37] in patients with CRSwNP [n = 161] vs −0.37 [−0.52 to −0.23] in patients without CRSwNP [n = 709]). These findings may be due to the association between comorbid CRSwNP, more extensive eosinophilic inflammation and/or IL-5 activity, and more severe disease in patients with severe eosinophilic asthma,[9] thus allowing greater room for improvement with targeted anti−IL-5 therapy among patients with versus without comorbid CRSwNP.

With regard to comorbid aspirin sensitivity, *post hoc* analyses have found that asthma exacerbation rates were reduced with anti−IL-5 therapy versus placebo in patients with severe eosinophilic asthma, irrespective of the presence/absence of NSAID-ERD or CRSwNP with aspirin sensitivity.[142,156] These findings further demonstrate improvements in asthma outcomes with anti−IL-5 therapy among patients with and without comorbid upper and lower airway disease.

Owing to the later clinical development of anti−IL-5/5R biologics for CRSwNP versus severe eosinophilic asthma, current evidence for the unified airway hypothesis based on these studies is less abundant than the evidence from asthma studies. Nonetheless, several important findings have been reported to date, which indicate both similarities and potential differences in the exact pathophysiology of asthma and CRSwNP. Interestingly, therapeutic targeting of the IL-5R has been shown to be less effective than targeting IL-5 in patients with a primary diagnosis of CRSwNP. Published studies of reslizumab in patients with a primary diagnosis of CRSwNP are limited. One small (N = 24) phase I study of reslizumab versus placebo has been reported,[56,160,161] but this was not designed or powered to detect treatment differences in efficacy outcomes. However, subgroup analyses of mepolizumab and benralizumab studies have found that patients with severe CRSwNP and comorbid asthma of any severity experience improvements in their asthma outcomes, including reductions in asthma exacerbations and clinically significant improvements in their asthma control with IL-5/5R inhibition versus placebo.[132,146,152,162]

With regard to sinonasal outcomes in patients with CRSwNP and comorbid lower airway disease, the significant improvements in total endoscopic NP score and sinonasal disease-specific QOL that were observed with mepolizumab versus placebo in the Effect of Mepolizumab in Severe Bilateral Nasal Polyps (SYNAPSE) study were larger among patients with versus without comorbid asthma or NSAID-ERD.[146] Conversely, significant improvements in sinonasal symptoms and SCS use were observed with mepolizumab versus placebo irrespective of the presence or absence of comorbid asthma or NSAID-ERD, and significant reductions in risk of surgery with mepolizumab versus placebo were larger among patients without comorbid asthma than among those with comorbid asthma.[146] In the Efficacy and Safety Study of Benralizumab for Patients With Severe Nasal Polyposis (OSTRO) study, benralizumab versus placebo significantly improved total endoscopic NP score and sinonasal symptoms versus placebo, but at the prespecified time point of 40 weeks did not significantly improve sinonasal disease-specific QOL; patients with comorbid asthma experienced larger improvements in total endoscopic NP score than those without.[132]

Interestingly, although no formal head-to-head comparison has been performed, targeting IL-5 with mepolizumab versus placebo appears to result in more substantial improvements across several clinically important CRSwNP outcomes than targeting the IL-5R with benralizumab (despite benralizumab reducing peripheral blood eosinophils to a larger degree than mepolizumab).[132,161] These outcomes include total endoscopic NP score, sinonasal symptoms, QOL, sinonasal surgery rates, and SCS use. One potential explanation is that airway tissue-resident eosinophils have a lower expression of transmembrane IL-5R and higher expression of soluble IL-5R than those found in the peripheral circulation[74,163]; this may cause eosinophils residing in the NP tissue to be less sensitive to anti−IL-5R therapy than those in the circulation, if receptor density is an important determinant of anti−IL-5R efficacy. However, further research is required to substantiate this speculation. Moreover, many inflammatory cells other than eosinophils express the IL-5R (Figure 3),[32,39,40,71,72,74-89] and further research is needed to fully understand the contribution of these cell types to CRSwNP pathophysiology and whether there is a differential regulation with anti−IL-5 or anti−IL-5R therapy. It should be noted that beyond differences in the treatments' mechanism of action, this discrepancy in efficacy results may also be due to variations in study design and the severity of disease among patients enrolled in the mepolizumab versus benralizumab trials.[132,161,164] Because treatment doses in these CRSwNP trials were based on those approved for patients with asthma (mepolizumab 100 mg subcutaneously; benralizumab 30 mg subcutaneously),[146,165] further research may be needed to establish optimal benralizumab dosing in patients with CRSwNP.

Because exposure to SCSs is associated with a risk of adverse health effects,[11,125,166,167] SCS reduction was an important clinical outcome in several clinical and real-world studies of anti−IL-5/5R biologics in patients with severe eosinophilic asthma or with CRSwNP. Studies of mepolizumab and benralizumab have shown reduced SCS use in patients with severe eosinophilic asthma and with CRSwNP.[115,144,146,153,168] In some of the studies, patients with comorbid upper and lower airway disease had significantly or numerically larger reductions in SCS dependence than those without[115,144,153,168]; however, in others, reductions in SCS dependence were observed irrespective of the presence/absence of comorbid upper and lower airway disease.[146] Taken together with the known mechanism of action for these treatments, the SCS-sparing data overall indicate that anti−IL-5/5R biologics can effectively alleviate some of the

clinical burden of type 2 inflammation in patients with airway disease, irrespective of whether the patient carries a primary diagnosis of asthma or CRSwNP, thus supporting the unified airway hypothesis.

Interestingly, dexpramipexole, a nonbiologic eosinophil-depleting drug that improved lung function in patients with severe eosinophilic asthma,[169] did not change NP size in a small open-label study in patients with CRSwNP.[170] This indicates that despite common elements, the pathophysiology of CRSwNP may be more complex than that of asthma.

Together, findings in the upper and lower airways demonstrate that although there may be differential efficacy between anti−IL-5 and anti−IL-5R biologics in patients with CRSwNP, therapeutic targeting of IL-5/5R for the treatment of severe eosinophilic asthma leads to improvements in both asthma and CRSwNP clinical outcomes (Figure 4). Similarly, therapeutic targeting of IL-5/5R in patients with CRSwNP can lead to improvements in CRSwNP and asthma outcomes, although the available evidence suggests potential differences in the roles and impact of IL-5 and the IL-5R in CRSwNP versus asthma pathogenesis. One limitation of these findings is that in several clinical trials in patients with asthma and comorbid CRSwNP, the presence of CRSwNP was identified using patients' medical records rather than performing sinonasal endoscopy and computed tomography scans prospectively. Nonetheless, available literature focused on the therapeutic targeting of the IL-5 pathway in a pathological setting supports upper and lower airway unification. This unified airway features a shared elevation of eosinophils and IL-5, perpetuating the chronic inflammation that underpins both severe eosinophilic asthma and CRSwNP.

CONCLUSIONS

Recent learnings on eosinophils and IL-5 further substantiate the unified airway hypothesis by demonstrating that they have important pathophysiological involvement in both upper and lower airway diseases. Moreover, pharmaceutical targeting of eosinophils and IL-5/5R and surgical intervention to remove NP tissue can lead to clinical benefits in both the upper and lower airways, thus supporting the hypothesis that airway diseases are best treated as a single condition manifesting in different locations. The exact roles of eosinophils and IL-5 in the pathophysiology of asthma and CRSwNP differ, and this is reflected by a disconnect between the observed efficacy of eosinophil and IL-5/5R-targeting biologics in asthma versus CRSwNP for some patients. Further research is therefore needed to better understand the pathophysiological link between eosinophils, IL-5, and the noneosinophilic effects of IL-5 in the manifestation of symptoms in upper and lower airway disease. Nonetheless, consideration of the unified airway hypothesis may aid disease management for patients diagnosed with comorbid upper and lower airway diseases, with complex care needs. Improved understanding of the pathophysiologic mechanisms of eosinophils and IL-5 in the unified airway, paired with data supporting the clinical benefits of their inhibition, could aid clinical decision making in practice.

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