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Biologics for the treatment of severe united airways disease**Nightingale Syabbalo MB., ChB., PhD., FCCP., FRS**

Professor of Physiology and Medicine, Nabanji Medical Centre, P. O. Box 30243, Lusaka-ZAMBIA

***Corresponding Author:** Nightingale Syabbalo MB., ChB., PhD., FCCP., FRS, Professor of Physiology and Medicine, Nabanji Medical Centre, P. O. Box 30243, Lusaka-ZAMBIA, Cell: +260 966 486117; Email: nightsyab@gmail.com

ID ORCID ID: <https://orcid.org/0000-0002-9435-5456>

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Abstract

The united airways disease refers to the coexistence of allergic rhinitis (AR), eosinophilic asthma, and chronic inosinate's with nasal polyps (CRSwNP). United airways diseases (UAD) are common inflammatory conditions, which contribute to significant morbidity, and economical costs. Eosinophilic asthma affects more than 50% of patients with asthma, and AR is the most common immunological disease. CRSwNP is a complex inflammatory disease affecting the nasal and paranasal sinuses, and is reported in approximately 4.3% of the general population. Eosinophilic asthma is often associated with AR, and CRSwNP, and share similar immunopathological mechanisms, characterised by eosinophilia, and raised immunoglobulin E. Patients with eosinophilic asthma and CRSwNP have very severe UAD, characterized by frequent exacerbations, hospitalisation, poor lung function, persistent nasal obstruction, and worse health-related quality of life. T helper type 2 (Th2) lymphocytes, and epithelial cells play an important role in the pathogenesis of eosinophilic asthma, AR, and CRSwNP. Activation of Th2 cells and epithelial dysfunction lead to secretion of cytokines, chemokines, and adhesion molecules which orchestrate airway eosinophilic inflammation. Th2 cytokines, such as interleukin-5 (IL-5), IL-4, IL-13, and epithelial-derived cytokines, including IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) play a key role in the pathogenesis of airway inflammation and remodelling. Treatment of severe united airways disease is difficult because of the severity of the syndrome. There is urgent need to develop novel biologics for uniform treatment of the UAD. Biologics targeting the inciting interleukins, such as mepolizumab and reslizumab (anti-IL-5), benralizumab (anti-IL-5R α), dupilumab (anti-4R α), and tezelizumab (anti-TSLP) have been shown to significantly reduce annualized exacerbation rates, improve asthma control, and lung function. Currently, there are two biologics which have been approved for the treatment of severe eosinophilic asthma and CRSwNP, including omalizumab, and dupilumab. Both biologics have been shown to concomitantly improve the nasal congestion score, Sino-Nasal Outcome Test-22 score, endoscopic nasal polyp score, Lund-Mackay computed tomography score, peak nasal inspiratory flow, and quality of life. Mepolizumab, reslizumab, benralizumab, and tezepelumab are in phase III clinical trials for the treatment of the UAD, and have been shown to be effective in the treatment of both severe eosinophilic asthma and CRwNP.

Keywords: Severe asthma; Allergic rhinitis; Chronic rhinosinusitis, Interleukins, Biologics

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Introduction

The united airways disease denotes the coexistence of allergic rhinitis (AR), eosinophilic asthma, and chronic rhinosinuitis with nasal polyps (CRSwNP) or without nasal polyps (CRsNP) [1-3]. United airways diseases (UAD) are common inflammatory conditions, which impacts considerable public health morbidity, and exorbitant economical costs. Eosinophilic asthma, allergic rhinitis (AR), and chronic rhinosinuitis (CRS) with nasal polyps or without nasal polyposis share similar histopathological, and immunopathological features characterized by eosinophilia, and elevated serum immunoglobulins E (IgE) [4,5]. The concept of the united airways disease (UAD) denotes that the upper and lower airways form a single organ, with upper and lower airways disease co-existing because they reflect different clinical manifestations of a single underlying disease process [6]. The possible mechanisms linking the upper and lower airways diseases include: aspiration of nasal inflammatory cells and mediators into the tracheobronchial tree, hematological dissemination of inflammatory mediators from one part of the airways to another, or nasotracheal reflexes [7]. The prototypical united airway diseases are asthma and allergic rhinitis, but pathophysiologic ally UAD is complex and heterogeneous, and may include clinical phenotypes of sinonasal disease, such as chronic rhinosinuitis with or without nasal polyps [8], and lower airway diseases, including, asthma-COPD overlap syndrome. Table 1 lists the diseases which comprise the united airways disease, and concomitant diseases. United airways diseases are common chronic inflammatory conditions, which contribute to substantial public health burden, and medical costs. The co-existence of severe,

uncontrolled asthma, and CRSwNP contributes to a severe UAD, characterized by poor asthma control, frequent exacerbations and hospitalization, poor lung function, and health-related quality of life (HLQoL). Similarly, patients with both diseases have severe nasal obstruction, persistent nasal discharge, posterior nasal drip, and facial pain which require intranasal budesonide irrigation, and repeated revision functional endoscopic sinus surgery (FESS). This review discusses the impact of sinonasal diseases on severity of asthma, and the role of interleukin antagonists (ILA) in the treatment of the united airways disease.

Table 1: Diseases comprising the united airways disease and concomitant diseases

United airways diseases Eosinophilic asthma Allergic rhinitis Chronic rhinosinuitis with nasal polyps Chronic rhinosinuitis without nasal polyps Aspirin exacerbated respiratory disease Asthma-COPD overlap
Concomitant diseases Chronic obstructive pulmonary disease Bronchiectasis Cystic fibrosis Obstructive sleep apnoea
Samter's Triad Eosinophilic asthma Chronic rhinosinuitis with nasal polyposis Aspirin exacerbated respiratory disease

Asthma

Asthma is a significant public health problem, affecting more than 358 million individuals globally [9], and its prevalence has been increasing in many countries worldwide during the last 40 years [9-11]. It is a chronic

inflammatory airway disease with distinct phenotypes, characterized by diverse immunopathological pathways, biomarkers of inflammation, and disease severity [12-16]. Asthma is classified into several cellular, molecular, and immunogenetic phenotypes [17,18], which respond differently to treatment, such as corticosteroids, and the new biologics. The four phenotypes of asthma, categorized on induced sputum cytometry, include eosinophilic, neutrophilic, mixed granulocytic, and paucigranulocytic asthma [13-19]. Approximately 40-60% of patients with severe asthma have eosinophilic phenotype [20-24]. Severe eosinophilic asthma often coexists with comorbidities, such as allergic rhinitis, CRSwNP, atopic dermatitis (AD), eosinophilic esophagitis (EoE), gastroesophageal reflux disease (GERD), obesity, and obstructive sleep apnoea (OSA) [25,26]. Most commonly eosinophilic asthma is associated with AR, and CRSwNP constituting the united airways disease. The term 'atopic march' denotes the orderly natural history of allergic disorders as they develop from infancy, and childhood from AD, progressing to food allergy, followed by AR and asthma, and finally to the fifth member EoE [27-32]. The coexistence of eosinophilic asthma, CRSwNP, and aspirin exacerbated respiratory disease (AERD) is termed as Sumter's Triad [33-37]. Immune cells, such as CD4⁺ T helper 2 (Th2) cells, and innate lymphoid group 2 cells (ILC2); haemopoietic cells, and non-haematopoietic cells, such as eosinophils, basophils, mast cells, and epithelial cells play a key role in the pathogenesis of eosinophilic asthma. Th2 lymphocytes, ILC2 cells, eosinophils, and mast cells secrete pro-inflammatory cytokines, such as IL-5, IL-4, and IL-13, which promote, immunoglobulin E synthesis, eosinophilia, mucus over production, airway hyperresponsiveness (AHR), and remodelling [38,39]. Additionally, airways epithelial cells contribute to allergic inflammation, AHR, and remodelling through epithelial-mesenchymal transition (EMT) [40-42], and secretion of 'alarmin' cytokines [43-45]. Damaged or dysfunctional epithelial cells secrete alarmin cytokines, such as IL-25, IL-33, and TSLP

which play master initiating role in the pathogenesis of eosinophilic asthma [46-50]. Furthermore, epithelial-derived cytokines stimulate Th2, and ILC2 cells, mast cells, basophils, and eosinophils to release large quantities of cytokines (IL-4, IL-5, IL-13, IL-25, IL-33, TSLP), chemokines (eotaxins 1-3, CXCL8, CXCL9, CXCL10, CXCL11, CXCL12, CCL17, CCL22), and growth factors (TGF- β 1, EGF-1, FGF, SCF, VEGF, angiopoietin, angiogenin). The liberated cytokines, chemokines, and growth factors promote airway inflammation, AHR, remodelling, and angiogenesis, which lead to severe airflow limitation [51,52].

Allergic rhinitis

Allergic rhinitis is the most common immunological disease with a prevalence of 10.1% and 15.3% in 6-7 years and 13-14 years old children, respectively [53], and about 26% adults in the United Kingdom [54]. The prevalence of the disease has increased over the past 4-5 decades worldwide, especially in industrial developing countries [55]. It is the most common chronic condition in children. Allergic rhinitis can be a very severe disease, and can reduce the health-related quality of life (HRQoL) [56]. In children it can interfere with attendance and performance at school [57,58], and in adults, it can lead to absenteeism from work, poor productivity, loss of earnings, and socio-economical costs [59]. Allergic rhinitis usually follows atopic dermatitis in the atopic march [27], and imposes a strong risk factor for subsequent development of asthma [1,2]. About 10%-40% of patients with rhinitis have asthma, suggesting the concept of "one airway, one disease" [10]. Similarly, about 74-81% of patients with asthma report symptoms of rhinitis [60]. Usually, allergic rhinitis precedes the development of asthma [61]. A longitudinal study has shown that children with allergic rhinitis before 5 years of age have a relative risk for asthma from 5-13 years of age about 3.82%, and 41.5% of children aged 5-13 with new onset wheezing had preceding allergic rhinitis [62]. Furthermore, the association between AR and asthma is associated with severe united

airways disease, and makes asthma control very difficult [63,64], and the treatment costly [64]. Treatment of allergic rhinitis significantly improves asthma control [65]. Rhinitis is inflammation of the nasal mucosa, characterized by nasal discharge (rhinorrhoea), nasal itching, sneezing, nasal blockage or congestion, post-nasal discharge, and facial pain [66,67]. Rhinitis has multifactorial causes, and clinically it is divided into allergic, non-allergic, infective, and mixed forms [4,66,67]. Allergic rhinitis is often accompanied by allergic inflammation of the conjunctivae (allergic rhinoconjunctivitis) [68]. It may also be associated with inflammation of the nasal and paranasal sinus mucosa (chronic rhinosinusitis with nasal polyps, or without polyps [69,70], otitis media [71], sleep-disordered breathing, and emotional problems [2]. Treatment of severe allergic rhinitis is difficult, particularly when it is associated with CRSwNP, and eosinophilic asthma. Many patients continue to have persistent symptoms, and a combination of treatment, such as non-sedating H1-antihistamines, intranasal corticosteroids, intranasal chromones, anti-cholinergic, anti-leukotrienes, and immunotherapy may be required in severe disease [72-74].

Chronic rhinosinusitis with nasal polyps

Chronic rhinosinusitis with nasal polyps is inflammation of the sinus and Para sinuses with growth of benign inflamed tissue (polyps) in the nasal cavity [75]. It is a common chronic condition which accounts for significant clinical burden and morbidity [76,77]. The prevalence of CRSwNP is about 10.9% to 13.4% of the general population in the European Union, and USA [78-80]. Crowns often coexist with asthma as united airway disease (UAD). The prevalence of CRSwNP in patient with asthma is about 7%, and as high as 35-45% in patients with severe, uncontrolled asthma [81,82]. Similarly, approximately 20-67% of patients with CRSwNP have asthma [83-85]. Nasal polyps are more common in severe, late-onset asthma, and usually precede the onset of asthma [86-90]. Patients with the

comorbid diseases have severe asthma and troublesome symptoms due to CRSwNP [91-93]. They have persistent airway inflammation and AHR, frequent exacerbations, hospitalization, and poor lung function, and worse HRQoL [94-99]. Furthermore, CRSwNP contributes to poor asthma control [26], and dependence on ICS or OCS. On the other hand, patients with CRSwNP and severe asthma have severe nasal obstruction, anosmia, sleep disturbances, anxiety, depression, and poor HRQoL [76,77,86-90, 100-102]. Patients with CRSwNP and asthma often become dependent on intranasal corticosteroids (INCS) or oral glucocorticoids, and require repeated revision sinus endoscopic surgery due to recurrence of nasal polyps [103-105]. Noteworthy, functional endoscopic sinus surgery (FESS) has been shown to improve asthma control and lung function; and to reduce the need for rescue inhaled medication, as well as ameliorate nasal symptoms [106,107]. The UAD is one of the most expensive disorders to treat and consumes substantial health care costs in developed countries [108,109]. Patients with severe eosinophilic asthma and CRSwNP have almost similar histopathological and immunopathological characteristics, such as eosinophilia, increased infiltration of eosinophils, mast cells, basophils, Th2 lymphocytes, group 2 innate lymphoid cells (ILC2), B cell, and plasma cells, with evidence of immunoglobulin E synthesis in the inflamed mucosa, and tissues [110-114]. Several chemoattractant chemokines which recruit eosinophils, neutrophils, Th2 lymphocytes, and B cells into inflamed nasal mucosa and tissues have been reported to be over-expressed or elevated in CRSwNP tissues. They include CCL2, CCL5, CCL7, CCL11, CCL13, CCL17, CCL18, CCL24, CCL26, CXCL12, and CXCL13 [115-118]. The recruited cells secrete a myriad of inflammatory cytokines, toxic cationic proteins, enzymes, reactive oxygen species which further orchestrate sinonasal inflammation, and remodelling, resulting in formation of nasal polyps [119]. Most patients with CRSwNP like eosinophilic asthma, have a Th2-mediated disease characterized by elevated biomarkers of eosinophilic

inflammation, such as raised Th2 cytokines IL-4, IL-13, and IL-5 [119-123]. Currently, there are few monoclonal antibodies targeting Th2 cytokines for precision treatment of severe eosinophilic asthma, such as omalizumab (anti-IgE), mepolizumab, erlizumab (anti-IL-5), erlizumab (anti-IL-5R), and dupilumab (anti-IL-4R α). However, only omalizumab and dupilumab have been approved for the treatment of eosinophilic asthma, allergic rhinitis, and CRSwNP. The airway epithelial cells play a central and an initiating role in the pathogenesis of the UAD through mesenchymal-epithelial transition (EMT), and by releasing 'alamin' cytokines, such as IL-25, IL-33, and TSLP. Patients with CRSwNP and severe asthma have elevated epithelial-derived cytokines in nasal polyp tissue, such as IL-25 protein, and IL-25 messenger RNA [124,125]; IL-33 and its receptor ST2 [126-128]; and TSLP expression and activity [129-133] compared with healthy individuals. Epithelial-derived cytokines stimulate IL-4, and IL-13 secretion from Th2 cells, and ILC2, which together with alarmin cytokines promote eosinophilic sinonasal inflammation, goblet hyperplasia, fibrin deposition, and remodelling [134]. Furthermore, IL-4 and IL-13 stimulate fibroblasts which produce extracellular matrix proteins, and secretion of pro-fibrotic matricellular proteins, such as periostin and osteopontin which promote nasal polyp formation [135]. Targeting TSLP with tezepelumab (TezspireTM) is very effective in the treatment of severe eosinophilic asthma, and other phenotypes of asthma without elevated eosinophilic counts, and fractional exhaled nitric oxide (FeNo). TezspireTM is a very suitable candidate biologic for targeted treatment of CRSwNP

Treatment of severe eosinophilic asthma

Most patients with asthma including eosinophilic phenotype respond to treatment with standard therapies, such as long-acting β -agonists (LABA), low-dose inhaled corticosteroids (ICS), long-acting muscarinic antagonists (LAMA) and/or leukotriene receptor antagonists (LTRA). Currently, there

are several single inhaler dual therapies, and single inhaler triple therapy (SITT) for maintenance treatment of patients with severe asthma. Triple therapy combination (LABA/LAMA/ICS) inhalers have been shown to significantly improve asthma symptoms control, reduce the frequency of moderate and severe exacerbations, and improve lung function compared with LAMA alone, and LABA/LAMA, or LABA/ICS single-inhaler dual therapy [136-139]. SITT inhalers, such as Trilogy Ellipta (FF/UMEC/VI) are very effective in the maintenance treatment of asthma [140], and convenient for the treatment of patients with severe asthma, and improve patient compliance [138]. Table 2 shows single inhaler dual therapy and single inhaler triple therapy combinations. Unfortunately, about 15-20% of patients with asthma remain uncontrolled, with frequent exacerbations, increased use of ICS or OCS, recurrent emergency room admissions, and poor health-related quality of life [141]. Furthermore, approximately, 3.6-10% asthmatics have severe refractory corticosteroid-resistant disease, which is uncontrolled despite treatment with high-dose ICS, LABA, and/or LTRA [142,143]. Treatment of severe, uncontrolled asthma is very costly, and is associated with significant socio-economic burden [144,145]. In the UK, severe refractory asthma accounts for about 50% of the health care budget for asthma due to high medication costs, hospitalization, intensive care admissions, and other healthcare utilization [145]. Although corticosteroids have been the mainstay of asthma therapy for many decades, they do not prevent progressive airway remodelling, and decline in lung function in patients with severe eosinophilic asthma. Furthermore, glucocorticoids are associated with serious adverse events [146]. Novel biologics are now available for targeted precision treatment of severe, uncontrolled eosinophilic asthma. Some of these biologics also ameliorate symptoms of CRSwNP, and improve HRQoL, and two have been repurposed for the treatment of CRSwNP.

Table 2: Single inhaler dual, and triple therapy combinations for the treatment of asthma, and chronic obstructive pulmonary disease

<p>Single inhaler dual therapy - LABA/LAMA Formoterol – Glycopyrrolate Formoterol – Aclidinium Vilanterol – Umclidinium Olodaterol – tiotropium Vilanterol - Umeclidinium Indaterol -Glycopyrronium</p> <p>Single inhaler dual therapy - LABA/ICS Salmeterol – Fluticasone propionate Formoterol – Beclomethasone dipropionate Formeterol – Budesonide Formeterol – Mometasone Vilanterol – Fluticasone IndaceroL – Mometasone</p>
<p>Single inhaler triple therapy - LABA/LAMA/ICS Beclomethasone dipropionate – Formeterol – Glycopyrronium Budesonide – Formoterol – Gylcopyrronium Fluticasone fuorate – Vilanterol – Umeclidinium</p>

Table 3: Monoclonal antibodies, and interleukin receptor antagonists, and their target.

Agent	Target	Phenotype	Stage of Development
OmaliZumab*	IgE	Th2	Marketed 2003
Mepolizumab*	IL-5	Th2	Marketed 2015
Reslizumab	IL-5	Th2	Marketed 2016
Benralizumab*	IL-5R	Th2	Marketed 2017
Dupilumab*	IL-4R α	Th2	Marketed 2018
Tezepelumab*	TSLP	Th2	Marketed 2018
Pitrakinra	IL-4R α	Th2	IIa
Lebrikizumab	IL-13R α 1	Th2	III
Tralokinumab	IL-13R α 1, 2	Th2	III
Brodalumab	IL-17RA	Th17	17 II
Secukinumab	IL-17A	Th17	17 II
Fezakinumab	IL-22	Th22	22 II
Etokimab	IL-33	Th2	2 IIa
Imatinib	c-kit receptor	Th2/Th17	II
Masitinib	c-kit receptor	Th2/Th17	II

Biologics still in phase 2 clinical trials have either been dropped out of the clinical trials for the treatment of asthma, or they are being investigated for the treatment of other allergic disorders.

*Approved for the treatment of childhood eosinophilic asthma.

Biologics for the treatment of eosinophilic asthma

There are several biologics targeting IgE, and interleukins which have been approved by the

Food and Drug Administration (FDA), and European Medicines Agent (EMA) for add-on maintenance treatment of severe, uncontrolled eosinophilic asthma [26]. They include omalizumab (anti-IgE) [147,148], mepolizumab (anti-IL-5) [149-151], erlizumab

(anti-IL-5) [152,153], benralizumab (anti-IL-5R) [154-156], dupilumab (anti-IL-4R α) [157,158], and tezepelumab (anti-TSLP) [159,160]. Mepolizumab, erlizumab, and dupilumab are also approved for treatment of severe eosinophilic asthma in children aged 6 years and older [161], whereas, tezepelumab is approved for treatment of severe eosinophilic asthma in paediatric patients aged 12 years and older [162]. All these biologics have been shown to improve asthma control, reduce exacerbations, improve lung function (FEV1), and HRQoL. Noteworthy, they allow patients to taper or discontinue corticosteroid therapy. Table 3 depicts approved biologics and those in development for the treatment of asthma and other allergic diseases.

Biologics for the treatment of eosinophilic asthma and chronic rhinosinusitis with nasal polyps

Currently, there are two biologics which have been approved by the FDA for the treatment of severe eosinophilic asthma, and coexisting CRSwNP. They include omalizumab [163], and dupilumab [164]. Both omalizumab [165-168], and dupilumab [169-172] have been shown to significantly improve the nasal congestion score, Sino-Nasal Outcome Test-22 (SNOT-24), sense of smell, centrally scored endoscopic nasal polyp score, Lund-Mackay computed tomography score, peak nasal inspiratory flow, and HRQoL. These biologics have had also been shown to improve sleep architecture, and reduce the need for intranasal corticosteroids. Dupilumab (Dupixent®) is a fully humanized IgG4 monoclonal antibody to the IL-4R α , which mediates signalling to both IL-4 and IL-13, hence, it blocks the downstream signalling, and immunopathological effects of both IL-4, and IL-13. Dupilumab was the first biologic licensed for the treatment of severe eosinophilic asthma and CRSwNP. It is the only biologic which ameliorates symptoms of most of the disorders in the atopic march [173]. Dupixent® is a universal biologic approved by the FDA for the treatment of severe eosinophilic asthma, CRSwNP, atopic dermatitis, and eosinophilic esophagitis. Mepolizumab [174,175],

reslizumab [176], benralizumab [177,178], and tezepelumab [179] are in phase III clinical trials, and have been shown to significantly improve nasal symptoms, anosmia, and HRQoL. In addition, mepolizumab has been demonstrated to reduce need for surgery for nasal polyps [180]. Tezepelumab (Tezspire™) is a first-in-class fully human IgG2 κ monoclonal antibody (mAb) that binds to TSLP, and prevents it to interact with its heterodimeric receptor TSLPR, thus inhibiting multiple downstream immunopathologic pathways, and production of cytokines, and chemokines [181,182]. It is the most impressive biologic for the treatment of severe asthma irrespective of phenotype, or levels of biomarkers of eosinophilic inflammation. It has been shown to reduce the annualized asthma exacerbation rates (AAER) by 71%, and improve lung function in patients with severe, uncontrolled asthma, irrespective of baseline blood eosinophil count, and fractional exhaled nitric oxide (FeNo) [183,184]. It has also been shown to reduce the biomarkers of eosinophilic inflammation, such as eosinophil count and FeNO [184,186]. Furthermore, the *post hoc* analysis of the PATHWAY study (NCT0205430) has shown that tezepelumab 210 mg every 4 weeks reduced the annualized asthma exacerbation rates to a similar extent in both patients with CRSwNP, and CRSsNP; 75% and 73%, respectively [186]. Patients who received Tezspire™ 210 mg also showed greater reduction in eosinophil count and the levels of FeNO, IL-5, and IL-13 compare with placebo-treated patients [186]. Recently, Menzie-Gow et al. [179] have shown that tezepelumab reduced the AAER by 86% in patients with CRSwNP, and by 52% in patients with CRSsNP, over 52 weeks, compared to placebo. Tezepelumab also increased lung function in both groups of patients. Patients with CRSwNP had an increase in pre-bronchodilator forced expiratory volume in one second (FEV1) of 0.2 L, whereas, patients with CRSsNP had increase in FEV1 of 0.13 L [179]. Treatment with tezepelumab also resulted in clinical improvement in nasal polyp symptoms at week 52. There was reduction in the Sino-nasal Outcome Test (SNOT-22) in patients with

CRSwNP by 9.6 points versus placebo. The baseline mean \pm standard deviation SNOT-22 score was 49.4 ± 21 for patients with CRSwNP, and 47.8 ± 19 for placebo-treated patients [179]. These results indicate that tezepelumab is effective and has the potential for the treatment of severe asthma, and severe CRSwNP.

Conclusion

The united airways disease refers to the coexistence of allergic rhinitis, eosinophilic asthma, and chronic rhinosinitis with nasal polyps. United airways disease contributes to significant morbidity and socio-economical costs. The coexistence of CRSwNP, and asthma contributes to severe, uncontrolled asthma, frequent exacerbation, hospitalization, and poor lung function, and HRQoL. Similarly, the comorbidity of severe asthma and CRSwNP is characterized by persistent nasal obstruction, and nasal discharge which require chronic INCS, antibiotics, and repeated endoscopic sinus surgery. Biologics targeting interleukins, such as omalizumab, mepolizumab, dupilumab, and tezepelumab are very effective in the treatment of severe, uncontrolled eosinophilic asthma. They are also very effective in ameliorating nasal symptoms in patients with asthma and coexisting CRSwNP. Currently, there are two biologics which have been approved by the FDA for the treatment of the UAD. They include dupilumab, and omalizumab, however, tezepelumab is a promising biologic for the treatment of the UAD.

Conflict of interest

The author declares that the publication was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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