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REVIEW

Established and Emerging Biological Therapies for the Treatment of Comorbid Asthma and Chronic Obstructive Pulmonary Disease

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Abstract: Asthma and chronic obstructive pulmonary disease (COPD) are two different and distinct airway disorders. However, some patients exhibit features of both, a condition often referred to as asthma-COPD overlap (ACO). Managing ACO is difficult because it is characterized by different inflammatory types and significant structural airway changes. Additionally, there is a lack of randomized controlled trials focusing specifically on ACO. Biologic therapies, originally developed for severe asthma and now increasingly studied in COPD, provide a precision-medicine approach by targeting cytokines and epithelial alarmins that contribute to type 2 (T2) and/or non-T2 inflammation. Current biologics, including anti-IgE, anti-IL-5, anti-IL-4Rα/IL-13, and anti-TSLP agents, are effective in the treatment of T2-high asthma and biomarker-driven COPD. This supports their use in ACO, especially for treating patients with eosinophilic or T2-dominant types. New therapies targeting IL-33/ST2, IL-17/IL-23, and dual blocking of epithelial alarmins show promise for influencing mixed inflammation profiles, though clinical evidence in ACO is limited. Selective IL-13 inhibitors exemplify pathway-specific treatment, but they are mainly suitable for T2-high subgroups. Despite promising mechanisms, evidence for biologics in ACO is mainly based on studies of asthma and COPD, and no drug is currently approved for this group. Future research should include ACO-specific clinical trials with adequate statistical power and endotype-guided patient selection. These trials should evaluate individual biologics, possibly using new endpoints such as airway remodeling, as well as mucus biomarkers, and omics-based phenotyping. These efforts will help develop personalized, mechanism-focused treatment plans that move beyond trial-and-error management and improve the role of biologics in ACO treatment.

Keywords: asthma, chronic obstructive pulmonary disease, asthma-COPD overlap, biologics

Introduction

Asthma-COPD Overlap: Definition, Burden, and Risk Factors

Asthma and chronic obstructive pulmonary disease (COPD) are among the most prevalent chronic respiratory diseases worldwide, affecting approximately 350 and 390 million individuals, respectively.[1,2] While asthma is classically defined by variable and reversible airway obstruction and COPD by persistent, largely irreversible airflow limitation, a subset of patients exhibits overlapping features of both disorders. This entity, termed asthma-COPD overlap (ACO), lacks a universally accepted definition, but it is increasingly recognized as a distinct clinically important phenotype of major public health significance.[3–5]

According to the Global Initiative for Asthma document, ACO is not a distinct disease entity, but rather it is a descriptive label applied to patients exhibiting features of both asthma and COPD in the context of persistent airflow limitation.[6] However, the criteria used to identify ACO differ depending on whether the condition is viewed primarily from an asthma- or COPD-focused perspective.[7,8] Definitions originating from COPD cohorts generally require a confirmed COPD diagnosis based on a post-bronchodilator forced expiratory volume in one second to forced vital capacity ratio (FEV_1/FVC) of less than 0.7, together with either a documented history of asthma before 40 years of age or

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a pronounced bronchodilator response, typically defined as an increase in FEV_1 of at least 15%.[7,9] In contrast, definitions derived from asthma cohorts typically rely on an established diagnosis of asthma combined with a substantial smoking history and evidence of fixed airflow obstruction, as indicated by a post-bronchodilator FEV_1/FVC ratio below 0.7.[10]

ACO is associated with older age, a history of smoking, environmental exposure (eg, biomass fuels, air pollution), and genetic predisposition.[11] Epidemiological studies indicate that smoking and air pollution significantly increase respiratory morbidity, with synergistic effects in ACO populations.[11] Additionally, recent work by Li et al demonstrates that ambient air pollution and genetic susceptibility interact to increase the risk of progression from asthma to COPD, further supporting the role of environmental and genetic factors in the development of ACO.[12]

Clinical Impact and Disease Burden

Patients with ACO experience greater symptom burden and worse outcomes than those with asthma or COPD alone. They are characterized by more frequent exacerbations, accelerated decline in lung function, and higher mortality.[13–15] Moreover, ACO is associated with increased healthcare utilization and reduced quality of life, posing a significant socioeconomic challenge.[13] The heterogeneous clinical presentation and inflammatory profiles complicate both diagnosis and management, highlighting the need for personalized approaches.[1]

Current Standard of Care and Limitations in ACO

The therapeutic cornerstone for asthma and COPD relies on inhaled medications, including inhaled corticosteroids (ICS), long-acting β_2-agonists (LABA), and long-acting muscarinic antagonists (LAMA).[1,2] While ICS/LABA combinations remain effective for asthma, dual bronchodilation (LABA/LAMA) is preferred for COPD, reserving ICS for patients with frequent exacerbations and elevated blood eosinophil counts (BECs).[16,17]

However, the optimal treatment strategy for ACO remains unclear, as patients with overlapping features are often excluded from clinical trials. Despite maximal inhaled therapy, many continue to experience exacerbations and persistent symptoms, underscoring a substantial unmet therapeutic need.[18,19]

Rationale for Biologic Therapy in ACO: Shared Type 2 Pathways

Advances in respiratory immunology have elucidated distinct inflammatory endotypes underlying asthma and COPD. In particular, type 2 (T2) inflammation, mediated by cytokines such as interleukin (IL)-4, IL-5, and IL-13, is a central mechanism of eosinophilic airway inflammation.[20,21] Biologic therapies targeting these pathways have revolutionized the management of severe asthma, especially in patients with high BECs, elevated fractional exhaled nitric oxide (FeNO), and increased T2 cytokine expression.[16,22–24]

Given the presence of shared T2 inflammatory pathways in subsets of COPD and ACO patients, biologics represent a mechanistically plausible and potentially effective therapeutic option.[25,26] Wechsler[22] highlighted that targeting T2-driven inflammation with monoclonal antibodies (mAbs) could improve outcomes in patients with overlapping asthma and COPD phenotypes.

Evidence from Established Biologics

Several biologics have shown efficacy in asthma, including anti-immunoglobulin E (IgE) (omalizumab), anti-IL-5 (mepolizumab, reslizumab), anti-IL-5 receptor alpha [IL-5Rα] (benralizumab), anti-IL-4Rα (dupilumab), and anti-thymic stromal lymphopoietin [TSLP] (tezepelumab)[1,16,23,24] (**Figure 1**). Dupilumab, targeting IL-4Rα and thereby blocking both IL-4 and IL-13 signaling,[27] became in 2024 the first biologic approved for eosinophilic COPD by both the European Medicines Agency (EMA)[28] and the US Food and Drug Administration (FDA).[29] Anti-IL-5 and anti-IL-5Rα therapies have also demonstrated reductions in COPD exacerbations among eosinophilic subgroups.[30,31] The FDA has approved mepolizumab for adults with COPD and an eosinophilic phenotype,[32] while the EMA is still reviewing the application and has not yet authorized it for this indication in Europe.

These findings suggest that biologics may be therapeutically beneficial for patients with ACO, as the overlapping mechanisms of ACO may render these agents particularly effective.[33] The PRISM project, a prospective, observational, multicenter cohort study of patients with severe asthma, found that the effectiveness of biologics in those with ACO was comparable to that

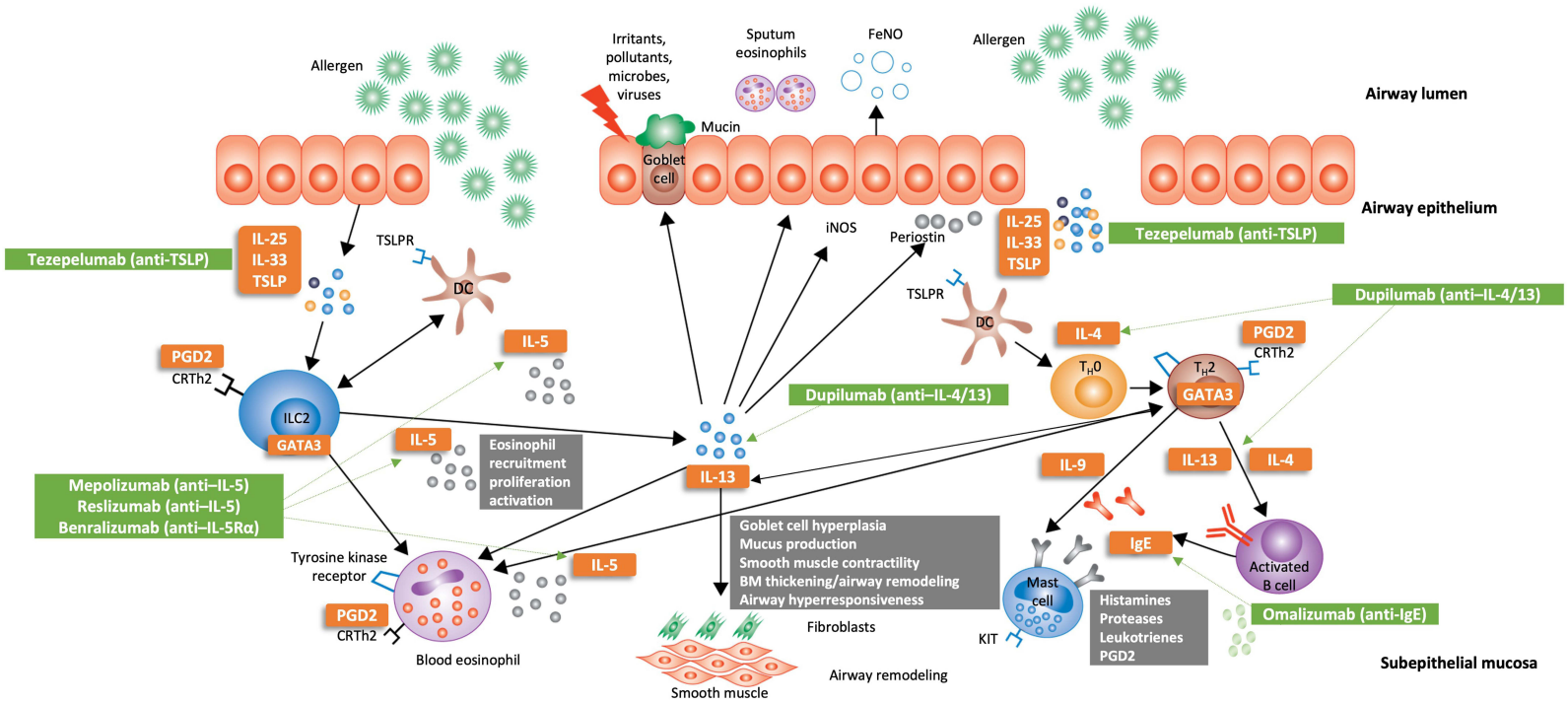

Figure 1 Immunopathology of type 2 inflammation and approved biologic therapies. Figure adapted from: Assaf SM, Hanania NA. Biological treatments for severe asthma. *Curr Opin Allergy Clin Immunol*. 2019;19(4):379–386.
Abbreviations: CRTH2, chemoattractant receptor homologous molecule expressed on TH2 cells; DC, dendritic cell; FeNO, fractional exhaled nitric oxide; GATAA3, GATA transcription factor; ILC2, group 2 innate lymphoid cell; KIT, proto-oncogene c-kit; PGD2, prostaglandin D2; Th0/Th2, T-helper cell; TSLP, thymic stromal lymphopoietin.

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observed in individuals with pure asthma alone. Therefore, the use of biologics can be considered in ACO guided by the general criteria for biologic therapy in severe asthma.[34] However, a recent French study involving 1949 patients with asthma and/or COPD found that only 29 patients (1.5%) had ACO with a BEC greater than 300 cells/μL, which would have made them eligible for biologics such as benralizumab, mepolizumab, and/or dupilumab.[35]

Knowledge Gaps

Despite rapid progress, several knowledge gaps remain. ACO patients continue to be underrepresented in clinical trials, leading to uncertainty regarding biologic efficacy, safety, and long-term outcomes in this population.[36,37] Moreover, the heterogeneity of inflammatory profiles, limited standardization of ACO diagnostic criteria,[36] and absence of validated biomarkers impede the implementation of personalized therapy.[36,38]

Review Goals and Focus

The present review aims to outline the immunopathological basis of ACO as a target for biologics, summarize current evidence on established and emerging mAbs in asthma and COPD, discuss biomarker-guided selection strategies, and highlight clinical implications, research challenges, and future directions for biologic therapy in patients with comorbid asthma and COPD.

Methods

Review Type

This article is a narrative, targeted review that synthesizes current evidence on biologic therapies in ACO and related phenotypes. The focus is on integrating immunopathology, biomarker-driven mechanisms, and clinical outcomes across asthma, COPD, and ACO populations.

Literature Search

A structured non-systematic search was conducted in PubMed, Embase, and Scopus covering January 2000 to November 2025. Search terms combined three domains: population ("asthma-COPD overlap", "ACO", "eosinophilic COPD", "T2-high COPD", "adult-onset asthma with fixed airflow limitation"), intervention ("biologic", "monoclonal antibody", "omalizumab", "mepolizumab", "reslizumab", "benralizumab", "dupilumab", "tezepelumab", "anti-IgE", "anti-IL-5", "anti-IL-4Rα", "anti-TSLP", "anti-IL-33"), and outcomes ("exacerbations", "FEV_1", "lung function", "quality of life", "steroid-sparing", "safety").

Additional sources included conference abstracts (American Thoracic Society [ATS], European Respiratory Society [ERS], Asian Pacific Society of Respirology [APSR], from 2018 to 2025) and regulatory documents (FDA, EMA). Reference lists of key publications were manually screened to capture additional relevant studies.

Scope of Evidence

The review focuses on adult populations (≥18 years) with ACO or proxy phenotypes, including eosinophilic COPD, adult-onset asthma with persistent airflow limitation, and mixed obstructive patterns with T2 inflammation. Evidence was drawn from randomized controlled trials (RCTs), post hoc analyses, observational cohorts, registries, and case series reporting clinical, biomarker, or mechanistic outcomes. Pediatric studies, in vitro or animal studies, and reports without relevant outcomes were excluded.

Biomarker Stratification

To contextualize therapeutic responses, evidence was interpreted according to biomarker-defined subgroups: eosinophilic phenotype (BEC ≥150–300 cells/μL), T2-high phenotype (FeNO ≥25 ppb or elevated composite T2 markers), and allergic phenotype (elevated serum IgE or confirmed sensitization). These thresholds guided interpretation but were not strict inclusion criteria.

Evidence Synthesis

Results were synthesized qualitatively, organized by biologic class (anti-IgE, anti-IL-5/IL-5Rα, anti-IL-4Rα/IL-13, anti-TSLP, anti-IL-33) and by disease phenotype or biomarker subgroup (eosinophilic, allergic, mixed). Asthma and COPD data were interpreted in the context of ACO pathophysiology. Overlapping cohorts were noted to avoid duplication.

Limitations

As this is a narrative review, we did not perform a formal risk-of-bias assessment, quality grading or meta-analysis. The focus was on integrating mechanistic rationale, biomarker-driven insights, and available clinical evidence to provide a comprehensive overview rather than a systematic quantification.

Shared and Distinct Immunopathology of Asthma, COPD, and ACO

Asthma, COPD, and their overlap (ACO) are characterized by distinct but sometimes overlapping airway inflammatory profiles that underpin differences in clinical presentation and treatment response. **Figure 2** summarizes these key immunopathological mechanisms.

Asthma Immunopathology

Asthma is characterized by chronic airway inflammation, airway hyperreactivity (AHR), and variable airflow limitation. Immunologically, it is generally classified as T2-high or non-type 2 (T2-low).[39]

In T2-high asthma, inflammation is largely eosinophilic and orchestrated by IL-4, IL-5, and IL-13, produced by Th2 CD4+ T-cells and group 2 innate lymphoid cells (ILC2s).[40] IL-4 and IL-13 promote B-cell class switching to IgE, mucus overproduction, and airway remodeling, whereas IL-5 supports eosinophil development, survival, and trafficking.[41] Key biomarkers include elevated BECs, sputum eosinophilia, FeNO, and total IgE.[42] Persistent eosinophilia may indicate non-allergic asthma endotypes, while spontaneous fluctuations in BEC suggest allergic phenotypes.[43]

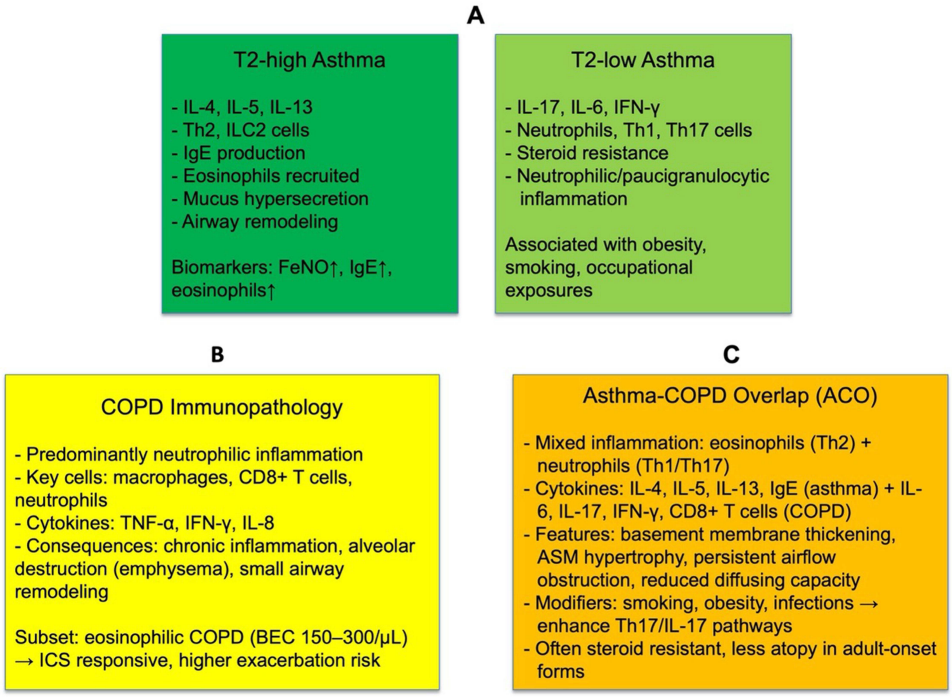

Figure 2 Immunopathological mechanisms in asthma, COPD, and asthma-COPD overlap (ACO). (**A**) T2-high vs T2-low asthma pathways. (**B**) COPD inflammatory profile. (**C**) Mixed inflammatory features in ACO.

Abbreviations: ASM, airway smooth muscle; BEC, blood eosinophil count; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; IFN-γ, interferon-γ; Ig E, immunoglobulin E; IL, interleukin; ILC2, group 2 innate lymphoid cells; TNF-α, tumor necrosis factor-α.

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In contrast, adult-onset asthma, particularly in patients with obesity, exposure to tobacco smoke or occupational irritants, or persistent airflow limitation, often presents as T2-low asthma. This phenotype is marked by increased neutrophils, upregulation of IL-17, IL-6, and interferon-γ (IFN-γ), CD8+ T-cell infiltration, or paucigranulocytic inflammation, and is frequently resistant to corticosteroid therapy, reflecting features more commonly associated with COPD.[20]

COPD Immunopathology

COPD is defined by irreversible airflow limitation resulting from chronic inflammation, emphysema, and small airway remodeling.[2] Inflammation is predominantly neutrophilic and is mediated by macrophages, $CD8^+$ T-cells, and Th1-type cytokines (TNF-α, IFN-γ, and IL-8).[44] However, a subset of COPD patients exhibits eosinophilic airway inflammation, with BECs of 150–300 cells/μL correlating with increased exacerbation risk and ICS responsiveness that suggests the presence of a T2-like inflammatory signature within COPD.[45,46]

Asthma-COPD Overlap

ACO exhibits heterogeneous inflammation, with both eosinophilic (T2) and neutrophilic (Th17/Th1) components.[47,48] This overlap is associated with airway remodeling (eg, basement membrane thickening, airway smooth muscle [ASM] hypertrophy), persistent airflow obstruction, and reduced diffusing capacity.[47,48] Environmental exposures (tobacco, obesity, infections) further amplify non-Th2 pathways such as Th17/IL-17-driven neutrophilia.[49] Notably, the absence of atopy and the corticosteroid resistance are more frequent in adult-onset ACO.[50]

Established Biologic Therapies in Severe Asthma and Their Relevance to COPD and ACO

Biologic therapies have transformed the management of severe asthma by providing targeted inhibition of immune pathways in patients whose symptoms are not adequately controlled by ICS and long-acting bronchodilators.[16] Although these therapies were initially developed for asthma, they are increasingly being investigated for use in patients with COPD and ACO due to shared or overlapping inflammatory mechanisms that support their potential efficacy. This section summarizes the clinical evidence for established mAbs and highlights their relevance to both COPD and ACO (Table 1).

Anti-IgE Therapy: Omalizumab

Mechanism of Action

Omalizumab is a recombinant humanized mAb that binds to the Cε3 domain of circulating IgE, preventing its attachment to high-affinity FcεRI receptors on mast cells and basophils.[51] This reduces the release of histamine, leukotrienes, and other mediators central to allergic airway inflammation. Chronic IgE neutralization also downregulates FcεRI expression on effector cells, leading to sustained attenuation of T2-high inflammatory pathways.

Evidence in Asthma

Omalizumab, the first anti-IgE biologic approved for treating severe allergic asthma, has been shown to reduce clinically significant exacerbations, decrease oral corticosteroid (OCS) dependence, and improve quality of life.[52–54] It is most effective in patients with elevated IgE and documented allergic sensitization. Long-term studies and registry data support the sustained benefits of omalizumab across a range of disease severities, highlighting its role as a cornerstone therapy for severe allergic asthma.

Evidence in COPD

Although omalizumab has not been evaluated in large COPD-specific RCTs, cohort analyses from COSYCONET and WISDOM suggest that elevated total serum IgE is associated with more frequent exacerbations and accelerated lung function decline, particularly in men.[55] These findings imply that IgE-mediated immune responses may contribute to disease activity in a subset of COPD patients. A study (NCT07059091) is currently investigating whether omalizumab benefits patients with COPD and coexisting allergic sensitization.

Table 1 Established Antibody Therapies in Severe Asthma and Their Application to COPD and ACO

Therapy	Mechanism of Action	Dose and Frequency	Evidence in Asthma	Evidence in COPD	Evidence in ACO	Clinical Implications
Anti-IgE (omalizumab)	Binds circulating IgE → prevents attachment to FcεRI on mast cells/basophils → ↓ histamine, leukotrienes, inflammatory mediators; downregulates FcεRI on effector cells	150–375 mg SC every 2–4 weeks, weight- and IgE-based	Reduces exacerbations (~26%), OCS dependence, improves QoL; sustained long-term benefits in severe allergic asthma	Elevated IgE linked to more frequent exacerbations and accelerated lung function decline; no large RCTs; ongoing trial NCT07059091	Real-world and post hoc studies show improved asthma control, QoL, ↓ exacerbations; limited spirometric improvement	Best for ACO with allergic sensitization and elevated IgE; minimal role in COPD without atopy; no formal ACO guidelines
Anti–IL-5/anti–IL-5Rα (mepolizumab, reslizumab, benralizumab)	Neutralize IL-5 (Mepolizumab/reslizumab) or IL-5Rα (benralizumab) → inhibit eosinophil maturation, survival, activation; benralizumab also induces ADCC-mediated eosinophil depletion	Mepolizumab: 100 mg SC q4w; reslizumab: 3 mg/kg IV q4w; benralizumab: 30 mg SC q4w ×3, then q8w	↓ exacerbations (~50%), OCS-sparing, improves FEV_1 and QoL	Mepolizumab: modest benefit (~18–20% ↓ exacerbations) in eosinophilic COPD; FDA-approved 2025; benralizumab: overall negative, potential benefit in high BEC and frequent exacerbations; reslizumab not studied	Reduce BECs, exacerbations, OCS use; no FEV_1 improvement; evidence largely extrapolated from asthma and eosinophilic COPD; in a real-life study, severe hospitalized exacerbations decreased more in ACO than in asthma alone	Consider for ACO with persistent eosinophilia and frequent exacerbations; smaller benefits in COPD; modest impact on lung function and QoL
Anti–IL-4Rα (dupilumab)	Blocks IL-4Rα → inhibits IL-4 and IL-13 signaling → ↓ T2 inflammation, eosinophils, FeNO, IgE, mucus, remodeling	400 mg SC loading, then 200 mg q2w OR 600 mg loading, then 300 mg q2w	↓ exacerbations, ↑ FEV_1, ↓ OCS use; efficacy across allergic/non-allergic T2-high phenotypes; comorbid AD and CRSwNP benefit	↓ moderate-to-severe exacerbations, prolonged time to first severe exacerbation in eosinophilic COPD (BEC ≥300); FDA and EMA approved 2024	No dedicated RCTs; post-hoc and real-world data show improvements in exacerbations, OCS dependence, FEV_1 in fixed obstruction (surrogate ACO)	Dual asthma and COPD approval makes it strong option for T2-high ACO; broad efficacy across eosinophilic phenotypes
Anti-TSLP (tezepelumab)	Blocks TSLP → inhibits activation of dendritic cells and downstream IL-4, IL-5, IL-13, and non-T2 pathways	210 mg SC q4w	↓ exacerbations 56–70% across asthma phenotypes, including low BEC/FeNO; ↑ FEV_1, asthma control, QoL; limited OCS-sparing effect	No significant reduction in moderate/severe exacerbations; subgroup analyses inconclusive	Case report: 71-year-old woman with severe ACO → tezepelumab + BLVR reduced exacerbations, improved symptoms and QoL over 2 years	Broad mechanism may be advantageous for ACO with mixed/low-T2 inflammation; further trials needed in COPD and ACO; potential option for difficult-to-treat phenotypes

Abbreviations: ACO, asthma-COPD overlap; AD, atopic dermatitis; ADCC, antibody-dependent cell-mediated cytotoxicity; BEC, blood eosinophil count; BLVR, bronchoscopic lung volume reduction; CRSwNP, chronic rhinosinusitis with nasal polyps; FcεRI, high-affinity Fc receptor for immunoglobulin E; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in one second; Ig E, immunoglobulin E; IL, interleukin; IV, intravenous; OCS, oral corticosteroid; QoL, quality of life; Rα, receptor alpha; RCT, randomized controlled trial; SC, subcutaneous; TSLP, thymic stromal lymphopoietin; T2, type 2 inflammation.

Evidence in ACO

Growing real-world evidence supports the use of omalizumab in ACO. In an Australian registry, patients with severe allergic asthma and COPD features experienced improvements in asthma control and health-related quality of life, although spirometric gains were limited in those with more pronounced COPD-related physiological impairment.[56] Similar reductions in exacerbations and hospital admissions have been described in small observational cohorts and case series.[57] A post hoc analysis of the multicentre observational PROSPERO study showed that ACO patients treated with omalizumab achieved reductions in exacerbation rates and improvements in Asthma Control Test scores comparable to those with asthma alone, regardless of the criteria used to define ACO; lung function remained stable over the 48-week follow-up.[58] Further supportive evidence arises from a secondary analysis of the EXTRA RCT, where omalizumab reduced exacerbations in patients with severe allergic asthma with or without fixed airway obstruction, but only the group exhibiting high bronchodilator reversibility, a phenotype encountered in ACO patients, showed particularly pronounced benefit.[59]

Clinical Implications

Although serum IgE did not significantly improve the mechanistic understanding of ACO, it can be used to categorize individuals with atopic and non-atopic ACO. This categorization could indicate different underlying biological processes and inform tailored therapeutic strategies.[60] In clinical practice, omalizumab represents a viable treatment option for patients with ACO who exhibit allergic sensitization, elevated serum IgE levels, and persistent exacerbations despite optimized inhaled therapy. These individuals appear most likely to benefit in terms of outcomes such as reduced exacerbations, improved symptom control, and enhanced quality of life. However, improvements in lung function may be limited in those with a predominant COPD pathophysiology. To date, no major respiratory society has issued formal recommendations for the use of omalizumab specifically in ACO. Prescribing decisions remain extrapolated from its established role in severe allergic asthma.

Anti-IL-5 and Anti-IL-5Rα Therapies: Mepolizumab, Reslizumab, Benralizumab

Mechanism of Action

IL-5 is a key regulator of eosinophil maturation, survival, and activation.[61] Mepolizumab and reslizumab are mAbs that neutralize IL-5, preventing its interaction with the IL-5R on eosinophils. Benralizumab binds IL-5Rα, inducing antibody-dependent cell-mediated cytotoxicity and resulting in near-complete eosinophil depletion.[62]

Clinical Evidence in Asthma

Substantial evidence supports the use of anti-IL-5/IL-5Rα therapies in severe eosinophilic asthma. In the DREAM trial, mepolizumab reduced exacerbations by ~48% compared with placebo,[63] and the SIRIUS trial confirmed its OCS-sparing effect in corticosteroid-dependent asthma.[64] Reslizumab has demonstrated significant reductions in exacerbations and improvements in lung function among patients with BEC ≥400 cells/μL.[36] Benralizumab decreased exacerbations by 50–70% and improved FEV_1 in the SIROCCO and CALIMA trials, with maximal efficacy in patients with BEC ≥300 cells/μL.[36] A Cochrane review confirmed that mepolizumab, reslizumab, and benralizumab reduce clinically significant exacerbations by approximately half, offering modest improvements in lung function and quality of life.[65] Current ERS/ATS guidelines recommend these therapies for severe eosinophilic asthma based on robust reductions in exacerbation risk and improved patient-reported outcomes.[66]

Evidence in COPD

The role of anti-IL-5 therapies in COPD remains debated.[67] Across several Phase 3 trials (METREX, METREO, and MATINEE[68,69]), mepolizumab (100 mg every 4 weeks) added to optimized triple inhaled therapy reduced annualized moderate or severe exacerbations by ~18–20% in patients with eosinophilic COPD (BEC ≥150 cells/μL at screening or ≥300 cells/μL in the prior year). Benefits were most pronounced at higher BEC thresholds, supporting a precision medicine approach. However, mepolizumab produced no consistent improvement in symptoms or health-related quality of life, and its effect on severe exacerbations requiring hospitalization remains uncertain.[31] Nonetheless, in May 2025, the FDA approved mepolizumab as add-on maintenance therapy for adults with inadequately controlled COPD and an eosinophilic phenotype.[32]

For benralizumab, the large GALATHEA and TERRANOVA trials did not show significant reductions in COPD exacerbations compared with placebo, even in patients with BEC ≥220 cells/μL.[70] Post hoc analyses suggest potential benefits in highly

selected subgroups with very high BECs and frequent exacerbations despite maximum inhaled therapy.[25] A recent randomized trial (ABRA) reported that a single dose of benralizumab (100 mg) during acute eosinophilic exacerbations of asthma or COPD (BEC ≥300/μL) reduced treatment failures compared with standard systemic corticosteroids.[71] However, the RESOLUTE Phase 3 trial did not meet its primary endpoint (the annualized rate of moderate or severe exacerbations in patients with three or more exacerbations in the previous year), despite numerical improvements.[72]

Evidence in ACO

Evidence for anti-IL-5/IL-5Rα therapy in ACO is limited. In elderly patients with ACO, mepolizumab significantly reduced BECs, exacerbation rates, and OCS requirements, although without measurable improvement in lung function.[73] These treatment responses were similar to those observed in patients with severe asthma alone. In practice, use in ACO is largely extrapolated from data in eosinophilic asthma and eosinophilic COPD,[66,74,75] although the Australian Mepolizumab Registry showed that mepolizumab significantly reduced exacerbations and improved symptom scores and lung function even in patients with ACO, which was considered a comorbidity among patients with severe eosinophilic asthma.[75] In a recent Belgian real-life study that examined patients with ACO (23.7% of the assessed cohort),[76] anti-IL5 therapy substantially reduced severe, hospitalized exacerbations from 119 to 53 per 100 patient-years (relative risk reduction [RRR] = −56%; number needed to treat [NNT] = 2). This reduction was compared with a decrease from 15 to 6 exacerbations per 100 patient-years in asthma alone (NNT = 11). Moderate OCS-treated exacerbations were reduced less consistently in ACO patients (RRR −8%, NNT = 7), while antibiotic-only exacerbations showed limited improvement. These results suggest that patients with ACO, who have higher baseline exacerbation rates, benefit greatly from anti-IL5 therapy. This therapy has the potential to prevent severe events in this high-risk population.

Clinical Implications

For patients with ACO who demonstrate persistent eosinophilic inflammation and frequent exacerbations despite optimal inhaled therapy, mepolizumab and benralizumab may be considered as add-on biologic options. Their expected benefits include reductions in exacerbation frequency, particularly at higher eosinophil counts, although improvements in lung function or quality of life are typically modest. In COPD, anti-IL-5 therapy provides meaningful but smaller benefits than in asthma, underscoring the need for careful phenotyping and biomarker-guided selection.

Anti-IL-4Rα Therapy: Dupilumab

Mechanism of Action

Dupilumab is a fully human mAb that targets the IL-4Rα subunit, which is a shared component of the receptor complexes for both IL-4 and IL-13.[27,77] By inhibiting IL-4Rα signaling, dupilumab broadly suppresses T2 inflammation, reducing eosinophilic airway inflammation, mucus hypersecretion, airway remodeling, and IgE class switching. Blockade of the IL-4/IL-13 axis also decreases FeNO, lowers blood and airway eosinophils, and improves epithelial barrier integrity.[77,78]

Clinical Evidence in Asthma

Dupilumab has demonstrated consistent efficacy across Phase 2b/3 asthma trials (eg, DRI12544,[79] LIBERTY ASTHMA VENTURE,[80] LIBERTY ASTHMA QUEST[81]). It reduces exacerbation frequency, improves lung function, decreases OCS use, and enhances asthma control and quality of life.[82] Although responses are greatest in patients with elevated BECs and/or FeNO, benefits are seen across a broad range of T2-high phenotypes. Its efficacy in comorbid atopic dermatitis and chronic rhinosinusitis with nasal polyposis (CRSwNP) further reflects its systemic T2-modulatory activity.[78]

Post-hoc analyses have clarified its role in both allergic and non-allergic asthma. One study showed that dupilumab improved lung function and reduced exacerbations regardless of allergic sensitization, while OCS-dependent patients achieved substantial reductions in steroid requirements.[82] Another study confirmed consistent improvements in exacerbation rates, pre-bronchodilator FEV_1, and asthma control scores in both allergic and non-allergic forms of moderate to severe asthma.[83] Taken together, these findings position dupilumab as a broad-spectrum biologic for T2-high asthma.

Evidence in COPD

Two pivotal Phase 3 trials (BOREAS[84] and NOTUS[85]) evaluated the use of dupilumab in patients with moderate to severe COPD who experienced recurrent exacerbations despite receiving optimized inhaled triple therapy and having eosinophilic inflammation. A pooled analysis of these trials showed that adding dupilumab significantly reduced the rate of annualized moderate to severe exacerbations and prolonged the time to first severe exacerbation in patients with BEC ≥300 cells/μL.[86] Biomarker analyses from the BOREAS trial documented greater reductions in T2 inflammatory markers (FeNO, total IgE, eotaxin-3, and pulmonary activation-regulated chemokine) with dupilumab and indicated that higher baseline BECs and FeNO levels were associated with greater treatment response.[87]

Based on these findings, both the European Medicines Agency (EMA)[28] and the FDA[29] approved dupilumab in 2024 as an add-on therapy for eosinophilic COPD that is not adequately controlled with standard inhaled treatment.

Evidence in ACO

No RCTs have specifically evaluated dupilumab in ACO.

Clinical Implications

The dual approval of dupilumab for asthma and eosinophilic COPD positions it as a promising therapeutic option for patients with ACO exhibiting T2-high eosinophilic inflammation. Evidence from post-hoc analyses and real-world cohorts suggests that patients with asthma and fixed airflow obstruction, often considered a surrogate for ACO, derive meaningful benefits. In the LIBERTY ASTHMA QUEST trial, dupilumab reduced severe exacerbations by up to 75% and increased the likelihood of reversing obstruction in patients with persistent airflow obstruction and high T2 biomarkers (BECs ≥ 150 cells/μL or FeNO ≥ 25 ppb).[88] Real-world studies, including a Dutch cohort[89] and an Italian registry,[90] have also reported substantial reductions in exacerbations, decreased OCS use, and improvements in FEV_1 and asthma control, even among patients with fixed obstruction or previous biologic treatment failure. These findings, along with dupilumab's documented efficacy in eosinophilic COPD, provide strong rationale for its use in ACO patients with T2-high eosinophilic features.

Anti-TSLP Therapy: Tezepelumab

Mechanism of Action

Tezepelumab is a fully human mAb that targets TSLP, an epithelial-derived alarmin that is rapidly released in response to allergens, viral pathogens, and airborne irritants.[91] TSLP initiates and amplifies airway inflammation by activating dendritic cells and promoting T2 immune responses. Increased TSLP expression has been well documented in the airway epithelium of patients with asthma, where it correlates with T2 chemokine production and greater disease severity.[91]

Emerging evidence also implicates TSLP in the pathophysiology of COPD. Increased TSLP levels have been observed in the airways of COPD patients, where they may influence local immune responses and contribute to chronic inflammation.[92] Key drivers of COPD inflammation and exacerbations, such as cigarette smoke and respiratory infections, induce TSLP overexpression, further supporting its role in exacerbation-prone COPD phenotypes.[92]

By neutralizing TSLP, tezepelumab blocks multiple inflammatory pathways, including IL-4, IL-5, and IL-13, as well as non-T2 mediators.[93] This upstream, pleiotropic mechanism distinguishes tezepelumab from biologics that target isolated pathways, such as IL-5 or IL-4/IL-13. This offers theoretical advantages in treating heterogeneous airway diseases in which multiple endotypes coexist.

Clinical Evidence in Asthma

Tezepelumab has demonstrated robust, broad-spectrum efficacy in treating severe, uncontrolled asthma.[93,94] In the PATHWAY (Phase 2b)[95] and NAVIGATOR (Phase 3)[96] trials, tezepelumab reduced annualized exacerbation rates by 56–70% versus placebo. These reductions were observed across the full spectrum of baseline BEC and FeNO levels, including in patients with low BEC (<150 cells/μL) and low FeNO. These are groups that typically respond suboptimally to other T2-directed biologics. Tezepelumab also produced consistent improvements in pre-bronchodilator FEV_1, asthma control, and quality of life.[94] A meta-analysis confirmed clinically meaningful benefits across allergic, eosinophilic, and non-eosinophilic phenotypes.[97] However, the SOURCE trial did not demonstrate a significant corticosteroid-sparing effect in OCS-dependent asthma,[98] suggesting a more favorable profile for reducing exacerbations than for withdrawing steroids.

Evidence in COPD

The Phase 2a COURSE trial evaluated the efficacy of tezepelumab in patients with moderate-to-very-severe COPD who had received 12 months of triple inhaled therapy.[99] The study did not meet its primary endpoint, as tezepelumab did not significantly reduce moderate-to-severe exacerbations compared with placebo over 52 weeks. Subgroup analyses across baseline BEC strata did not identify a patient population with a consistent response. It has been suggested that the inclusion of GOLD 2 patients, many of whom were adequately managed with dual bronchodilation, may have limited the ability to detect clinical benefit.[100] Therefore, although the concept of upstream airway modulation remains attractive, the evidence for its use in COPD is inconclusive.

Evidence in ACO

Tezepelumab has not been formally evaluated in clinical trials targeting ACO. However, case-based evidence provides preliminary insights into its potential utility. A recent report described a 71-year-old woman with severe ACO, characterized by frequent exacerbations and persistent hyperinflation despite optimized triple inhaled therapy.[101] Sequential treatment with tezepelumab, followed by bronchoscopic lung volume reduction (BLVR), resulted in marked clinical improvement. Tezepelumab reduced exacerbation frequency and improved symptom control, while BLVR addressed refractory hyperinflation. Over two years, the patient experienced sustained gains in lung function, quality of life, and annual exacerbation rate. This case underscores the potential value of combining upstream anti-inflammatory therapy with interventional approaches in difficult-to-treat ACO.

Clinical Implications

Tezepelumab is the first biologic to demonstrate efficacy across asthma phenotypes, including those with low T2 biomarkers. Its broad mechanism may be advantageous for ACO, where patients often exhibit complex and overlapping inflammatory signatures. However, without clinical data on ACO and with inconclusive results on COPD, its role remains theoretical. Future studies focusing on fixed obstruction, mixed inflammatory profiles, and eosinophil-independent disease mechanisms are essential to determining whether tezepelumab can fulfill its potential as a versatile biologic across the spectrum of obstructive airway diseases.

Emerging Biologic Therapies with Potential Application in ACO

The awareness that anti-IL-5/IL-5Rα, anti-IL-4Rα/IL-13, and anti-TSLP mAbs are the leading biologic treatments for obstructive airway diseases is supporting the development of numerous other mAbs for asthma and COPD. Their mechanisms imply potential importance for ACO, especially given the varied and overlapping inflammatory endotypes present in this population (Table 2).

Anti-IL-5 and Anti-IL-5Rα Therapies

Depemokimab is an ultra-long-acting, humanized IgG1 mAb targeting IL-5, engineered to maximize binding affinity and extend serum half-life, allowing twice-yearly subcutaneous dosing.[102] Its clinical development program has primarily focused on severe eosinophilic asthma[103] and CRSwNP,[104] conditions characterized by persistent T2 inflammation and elevated blood eosinophils. Completed trials have excluded patients with a primary diagnosis of COPD or ACO. However, depemokimab is now being investigated in two Phase 3 trials, ENDURA-1 and ENDURA-2 (NCT06961214), designed to assess its efficacy and safety as an add-on therapy for adults aged 40–80 years with moderate to severe COPD and evidence of T2 inflammation, defined by elevated blood eosinophils, a history of exacerbations, and optimized inhaled therapy. These trials will clarify whether durable IL-5 inhibition can reduce exacerbations in eosinophilic COPD and, by extension, could offer therapeutic benefit to patients with ACO who share similar inflammatory characteristics.

Anti-TSLP Therapy: Verekitug

Verekitug is a fully human recombinant IgG1 mAb that targets the TSLP receptor (TSLPR) rather than the TSLP ligand itself.[105] Early in silico modeling suggests that TSLPR blockade may produce more sustained inhibition of biomarkers

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Table 2 Emerging Biologic Therapies with Potential Application in ACO

Therapy	Mechanism of Action	Evidence in Asthma	Evidence in COPD	Evidence in ACO	Clinical Implications
Anti-IL-5/anti-IL-5Rα (depemokimab)	Ultra-long-acting mAb against IL-5; high binding affinity and extended half-life; subcutaneous dosing every 6 months-	Phase 1 and 3 trials: effective in severe eosinophilic asthma with elevated eosinophil counts; improves exacerbation control	Being evaluated in Phase 3 ENDURA-1 and ENDURA-2 (NCT06961214): adults 40–80 with moderate-to-severe COPD, T2 inflammation, high eosinophils, frequent exacerbations, optimized inhaler therapy.	No direct studies yet. Biological plausibility in eosinophilic/T2 ACO given overlapping mechanisms.	Potential long-interval add-on therapy for eosinophilic T2-driven disease; may reduce treatment burden vs monthly dosing.
Anti-TSLP (verekitug)	Fully human IgG1 mAb targeting the TSLP receptor (vs ligand); stronger, longer suppression of FeNO and biomarkers due to receptor turnover kinetics.	Phase 1b: ↓ FeNO & BEC sustained up to 24 weeks; VALIANT & VALOUR trials (NCT06196879, NCT06966479) evaluating long-term efficacy/safety in severe asthma.	VENTURE trial (NCT06981078) assessing efficacy and safety in COPD patients.	Biologically plausible benefit in T2/eosinophilic ACO, though no direct trials.	Potential for extended dosing intervals (up to 24 weeks) vs standard monthly biologics; may broaden applicability across T2-driven asthma, COPD, and ACO.
Anti-IL-33 (itepekimab, etokimab, tozorakimab)	Block IL-33, an epithelial alarmin driving T2 (IL-5, IL-13) and non-T2 inflammation; reduces remodeling; enhances antiviral immunity.	No published phase 2/3 efficacy data yet.	Itepekimab: ↓ exacerbations and ↑ lung function in former smokers (phase 2b); no effect in current smokers.	Efficacy in ACO not yet proven	Rationale for targeting IL-33 in mixed ACO phenotypes: 1. high IL-33 linked to dual eosinophilic/neutrophilic inflammation, 2. eosinophils in ACO show ↑ ST2 expression.
Anti-ST2 (astegolimab)	Blocks IL-33 receptor (ST2) expressed on ILC2s, T cells, mast cells, eosinophils, macrophages.	↓ exacerbations in severe asthma (even with low eosinophils); no lung function improvement.	No ↓ in COPD exacerbations; modest benefits in health status and eosinophil reduction.	No direct studies.	Potential add-on in mixed-inflammation ACO; further ACO-specific trials required.
Anti-IL-17/anti-IL-23 pathway	Blockade of IL-23/IL-17 axis → ↓ neutrophilic inflammation, remodeling, AHR.	Risankizumab worsened outcomes; Brodalumab trial stopped for futility.	CNTO-6785 (anti-IL-17A): no efficacy; preclinical models suggest benefit in neutrophilic COPD.	IL-17 blockade reduced remodeling/ obstruction in experimental ACO models.	May help non-T2 ACO phenotypes; current human data weak.

Dual IL-33/ TSLP blockade (eg, HXN-1013)	Bispecific antibodies target both IL-33 and TSLP → block overlapping T2 & non-T2 cascades.	No trials yet	No trials yet.	No studies; rationale strong given overlapping inflammatory drivers.	Promising broad-spectrum approach; needs phenotype-stratified ACO trials.
Anti-TSLP/IL-4Rα dual targeting (ZW1528)	IgG-like bispecific molecule binding IL-33 and IL-4Rα; blocks both T2 (IL-4/IL-13 axis) and non-T2 (IL-33-driven) inflammation.	Not yet tested in asthma patients.	In vitro: suppressed T2 and non-T2 responses in immune cells from COPD patients; effective in murine COPD models.	No direct trials in ACO, but mechanistic rationale strong due to mixed T2/ non-T2 inflammatory drivers.	Could provide broader control across overlapping inflammatory pathways; promising for mixed ACO phenotypes, pending clinical validation.
Anti-TSLP/anti-IL-13 dual targeting (lunsekimig)	Bispecific nanobody molecule that blocks both TSLP and IL-13.	Single-dose administration well tolerated and associated with rapid and significant reductions in FeNO, BECs, and other T2 biomarkers, as well as improvements in lung and small airway function	No studies conducted to date.	No direct studies, but mechanistically plausible benefit.	Potential to enhance airway function and reduce exacerbations in ACO patients with predominant T2 inflammation
Anti-IL-13 (tralokinumab, lebrikizumab, eblasakimab)	Block IL-13 → ↓ goblet cell metaplasia, mucus hypersecretion, AHR, fibrosis, remodeling. Eblasakimab: first-in-class mAb targeting IL-13Rα1, blocking downstream STAT6 phosphorylation and reducing T2 signaling.	Modest efficacy. Biomarker-enriched subgroups (periostin, FeNO, IgE) respond better.Early-phase studies: demonstrated IL-13Rα1 blockade and STAT6 inhibition with single IV (3 mg/ kg) and SC (300 mg) doses; no serious TEAEs reported.	No efficacy in COPD.	Likely benefit in T2-high ACO with eosinophilia, high FeNO, periostin, mucus-driven disease.	Useful in biomarker-selected T2-high ACO subgroups; not universal.

Abbreviations: BEC, blood eosinophil count; FeNO, fractional exhaled nitric oxide; Ig E, immunoglobulin E; IL, interleukin; STAT6, signal transducer and activator of transcription 6; Rα, receptor alpha; ST2, suppressor of tumorigenicity 2; TSLP, thymic stromal lymphopoietin; T2, type 2 inflammation.

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such as FeNO than ligand neutralization, potentially due to lower receptor expression levels and slower receptor turnover.[106] A Phase 1b study in 32 adults with asthma demonstrated that subcutaneous verekitug produced sustained reductions in FeNO and blood eosinophils lasting up to 24 weeks after the final dose.[107] These durable pharmacodynamic effects may ultimately allow for extended dosing intervals (eg, every 12–24 weeks), in contrast to the every-4-week schedule of tezepelumab.

Verekitug is currently being evaluated in multiple clinical trials. The VALIANT trial (NCT06196879) is assessing the efficacy and safety of different dosing intervals (every 12 vs every 24 weeks) for up to 60 weeks in adults with severe asthma. VALOUR (NCT06966479) is an extension study evaluating the long-term safety and effectiveness of verekitug in adults who completed VALIANT. The VENTURE study (NCT06981078) is investigating verekitug in patients with COPD, reflecting growing interest in targeting upstream epithelial-derived cytokines in obstructive airway diseases. Based on the known role of TSLP in both asthma and COPD pathobiology, and given the mixed inflammatory patterns typical of ACO, it is biologically plausible that verekitug may have therapeutic potential for ACO patients with T2/eosinophilic inflammation. However, no studies have yet specifically evaluated its efficacy in this population. The extended dosing schedule could be particularly advantageous for older adults or those with multimorbidity, common characteristics in ACO.

Anti-IL-33 Therapy: Itepekimab, Etokimab, Tozorakimab

IL-33, an epithelial-derived alarmin, is released in response to airway injury and activates both innate and adaptive immune pathways. IL-33 amplifies T2 inflammation by promoting IL-5 and IL-13 production. It also contributes to non-T2 responses, airway remodeling, and heightened susceptibility to exacerbations.[108,109] In experimental models of chronic airway disease, IL-33 blockade reduces persistent inflammation, attenuates structural remodeling, and restores epithelial integrity, features that directly relate to exacerbation risk in asthma, COPD, and ACO.[110,111] Furthermore, IL-33 inhibition enhances antiviral immunity, which is relevant for virus-induced exacerbations commonly observed in overlap syndromes.[112]

Among the emerging biologics targeting IL-33, itepekimab has shown potential benefits in the treatment of COPD, particularly in former smokers. In a Phase 2a trial, itepekimab added to standard therapy reduced exacerbations and improved lung function in this group.[113] These benefits were diminished or absent in current smokers, likely due to lower IL-33 expression.[114] The effect was independent of baseline eosinophil count, although FEV_1 improvements were greater in patients with higher eosinophil levels. Etokimab, another anti-IL-33 mAb, has undergone early-phase evaluation in atopic dermatitis,[115] but there is presently no published evidence supporting its efficacy in asthma, COPD, or ACO. Tozorakimab is a high-affinity mAb that binds directly to and neutralizes IL-33. This prevents IL-33 from activating its downstream signaling pathways, including those mediated by suppressor of tumorigenicity 2 (ST2) and the receptor for advanced glycation end products/epidermal growth factor receptor (RAGE/EGFR) complex. Tozorakimab has demonstrated potent biological activity in preclinical models, including suppression of ST2-dependent inflammatory responses and mitigation of lung epithelial injury.[116] In a Phase 1 clinical study of COPD patients, tozorakimab significantly reduced circulating downstream T2 cytokines such as IL-5 and IL-13. This suggests activation of T2-associated pathways, which may be relevant in eosinophilic COPD and ACO.[117]

From an ACO perspective, mechanistic data strongly support IL-33-targeted therapy. Eosinophils from patients with ACO and eosinophilic COPD exhibit increased IL-33-induced upregulation of ST2, also known as interleukin 1 receptor-like 1 (IL1RL1), which highlights the importance of IL-33 signaling in these conditions.[118] Moreover, the correlation between high IL-33 expression and exacerbation risk, coupled with the frequent coexistence of eosinophilic and neutrophilic inflammation in ACO patients,[108,109,119] underscores the role of IL-33 as a key upstream driver in overlap disease. Taken together, these findings suggest that inhibiting the IL-33 pathway is a promising therapeutic strategy for ACO. Further clinical studies, particularly in eosinophilic or biomarker-enriched populations, are needed to assess whether IL-33 blockade can provide meaningful clinical benefits to this heterogeneous and undertreated group.

Anti-ST2 Therapy: Astegolimab

ST2 is the primary receptor for IL-33 and is expressed on multiple immune cell types, including ILC2s, $CD4^+$ and $CD8^+$ T cells, basophils, mast cells, eosinophils, and macrophages.[120] Genetic studies have consistently identified both IL-33 and ST2 as susceptibility loci for asthma, and increased IL-33/ST2 expression correlates with greater disease severity and exacerbation risk.[121] In COPD, the expression of IL-33 and ST2 in airway and lung tissue is similarly upregulated, particularly in response to cigarette smoke.[122] This increased expression is associated with enhanced T2 inflammation, alveolar damage, and accelerated disease progression. Beyond classical allergic pathways, IL-33/ST2 signaling also regulates non-T2 inflammation, tissue repair, and host defense mechanisms, supporting its relevance across diverse airway endotypes.[123]

Astegolimab, a mAb that targets the ST2 receptor, thereby inhibiting IL-33 signaling, has been investigated for its potential to treat severe asthma[124] and COPD.[125] In asthma patients, astegolimab produced modest yet significant reductions in annual exacerbation rates, even in those with low baseline BECs. However, it did not improve lung function parameters. In COPD patients, astegolimab did not significantly reduce the annual exacerbation rate compared to placebo. However, the treatment was associated with reduced BECs and statistically significant improvements in patient-reported health status. Astegolimab also reduced blood and sputum eosinophil counts. Its clinical benefit was not restricted to patients with eosinophilic inflammation, suggesting potential value in subgroups with mixed or T2-inflammatory features. Since IL-33/ST2 signaling contributes to both eosinophilic and neutrophilic inflammation, which are common patterns in ACO, astegolimab may be therapeutically beneficial for select ACO phenotypes. Patients with overlapping T2 and non-T2 inflammatory signatures or persistent exacerbations despite standard therapy may theoretically respond to ST2 inhibition. Nevertheless, dedicated studies in ACO populations are required to clarify the clinical utility of astegolimab and define appropriate biomarker-based patient selection criteria.

Anti-IL-17 and Anti-IL-23 Pathway Therapies

The IL-23/IL-17 signaling axis has emerged as a key regulator of chronic airway inflammation. IL-23 promotes the development and survival of Th17 lymphocytes, which leads to the production of IL-17A and other cytokines. This cascade drives neutrophil recruitment and, to a lesser extent, eosinophilic activity. It also contributes to airway remodeling and AHR. In asthma, particularly in severe or corticosteroid-refractory cases, increased IL-23/IL-17 activity is associated with neutrophilic inflammation and decreased lung function, reflecting a mechanistic link between the severity of the disease and this pathway.[126,127] Similarly, in COPD, elevated IL-17A and IL-23 levels correlate with persistent airway inflammation, structural remodeling, and frequent exacerbations, with pathway activity further intensified during infection-driven episodes.[128,129] Preclinical evidence underscores the functional relevance of this axis. Neutralizing IL-17A in animal models mitigates neutrophilic infiltration and restores airflow, confirming its role in chronic airway injury.[130] Notably, macrophages, rather than T-cells, appear to be the dominant cellular source of IL-23R expression in allergic airway inflammation.[131] This finding highlights the role of innate immune cells in non-T2 airway disease.

Despite the strong mechanistic rationale, clinical translation of IL-23 and IL-17-targeted therapies has proven disappointing. In asthma, the anti-IL-23 mAb risankizumab failed to improve outcomes and was paradoxically associated with accelerated worsening and higher exacerbation rates compared to placebo.[132] Similarly, brodalumab, which inhibits IL-17RA, did not improve asthma control or lung function in the overall population.[133] There was only a nominal signal in a small, high-reversibility subgroup, which was not confirmed in subsequent studies (NCT01902290). In COPD, experimental data suggest that blocking IL-17A may reduce neutrophilic recruitment and shift the inflammatory profile toward a more controlled anti-inflammatory immune response. This could preserve structural integrity[134] and improve outcomes during infectious exacerbations.[135] However, clinical efficacy remains unproven. In a randomized, placebo-controlled phase 2 trial of patients with moderate-to-severe COPD, brodalumab showed no statistically or clinically significant improvement in lung function or other endpoints compared to placebo.[136] These findings suggest that, although IL-17A signaling is mechanistically active, it is not a predominant driver of COPD pathophysiology.

Translational challenges likely arise from species-specific differences in immune regulation, the complexity of airway inflammatory networks, and the heterogeneity of disease endotypes. Nevertheless, IL-23/IL-17 inhibition is conceptually

relevant for non-T2 phenotypes, particularly in ACO, where neutrophilic and mixed inflammatory patterns coexist. Supporting this notion, Camargo et al demonstrated in an experimental ACO model that IL-17 blockade attenuated extracellular matrix remodeling and airway obstruction.[137] This suggests a potential therapeutic benefit in phenotypes characterized by combined eosinophilic and neutrophilic inflammation. These findings highlight the importance of further investigation of IL-23/IL-17-targeted therapies in ACO and the need for precision phenotyping to identify the most responsive subgroups.

Anti-TSLP/IL-4Rα Dual Targeting

ZW1528, an IgG-like bispecific antibody engineered to target both IL-33 and IL-4Rα simultaneously, is a promising addition to the evolving field of airway immunomodulation.[138] Blocking IL-4Rα inhibits Th2-driven eosinophilic inflammation, IgE production, and AHR, while blocking IL-33 reduces persistent airway inflammation, remodeling, and exacerbation risk by acting on both innate and adaptive immune cells. ZW1528 attenuates T2 and non-T2 immune responses in primary cells derived from COPD patients in vitro, suggesting that the molecule can modulate complex inflammatory networks that extend beyond the classical eosinophilic pathways. In vivo, ZW1528 demonstrates efficacy in acute and chronic murine models of house dust mite-driven airway inflammation by reducing the inflammatory burden and improving physiologic outcomes. These dual-targeting properties are highly relevant to ACO, where overlapping T2 and non-T2 mechanisms often coexist, complicating therapeutic decision-making. By converging on two mechanistically upstream nodes of airway inflammation, ZW1528 may offer broader control across endotypes than single-pathway biologics. Although clinical data are not yet available, the preclinical characteristics of ZW1528 suggest its potential relevance not only for COPD but also for the mixed-granulocytic or "hybrid" inflammatory profiles frequently encountered in ACO.

Anti-TSLP/IL-33 Dual Targeting

Bispecific antibodies and strategies involving the sequential blockade of epithelial alarmins such as TSLP and IL-33 are now in the early stages of development. This reflects a shift toward the upstream suppression of both T2 and non-T2 inflammatory initiation. HXN-1013, a bispecific molecule, binds simultaneously to TSLP and IL-33. This prevents each cytokine from binding to its respective receptor, thereby disrupting two central epithelial "danger" signals implicated in amplifying airway inflammation.[139] In a peripheral blood mononuclear cell activation system co-stimulated with TSLP and IL-33, HXN-1013 showed superior inhibitory activity compared to either parent antibody alone. This finding underscores the potential for additive, or even synergistic, benefits from concurrent upstream blockade.

From an ACO perspective, the bifunctional inhibition of IL-33 and TSLP is especially compelling because it offers a theoretically broader, more integrated form of immunomodulation than single-target approaches. Such upstream control could dampen multiple converging cascades, thereby addressing the heterogeneous pathophysiology of ACO more holistically. However, this promise remains speculative pending clinical validation. No large-scale, phenotype-stratified trials have evaluated the bispecific or combined IL-33/TSLP inhibition in ACO. The true therapeutic impact of this strategy, particularly across diverse inflammatory phenotypes, remains to be fully delineated.

Anti-TSLP/anti-IL-13 Dual Targeting

Lunsekimig (SAR443765) is a bispecific nanobody designed to inhibit both TSLP and IL-13 simultaneously.[140] Nanobodies, derived from the single-domain antibody fragments of camelid heavy-chain-only immunoglobulins, provide distinct structural and functional advantages, including compact size, high binding affinity, physicochemical robustness, and efficient microbial or genetic production.[141] These advantages make nanobodies attractive therapeutic platforms. In the first-in-human study of lunsekimig for asthma treatment, a single dose was well tolerated with no clinically meaningful immunogenicity.[142] The pharmacodynamic effects were rapid and pronounced. Reductions in FeNO, BECs, and other T2 inflammation biomarkers were accompanied by improvements in both global and small-airway function. These preliminary findings suggest that dual inhibition of TSLP and IL-13 may suppress T2 pathways more broadly and effectively than targeting a single cytokine alone. From a conceptual standpoint, the implications for ACO are noteworthy. By intercepting both the initiation (TSLP) and effector (IL-13) arms of T2 immunity, lunsekimig may more comprehensively attenuate the epithelial-immune axis

characteristic of T2-high ACO phenotypes. This dual inhibition has the potential to enhance control of airway dysfunction and reduce exacerbation risk in patient subsets where T2 inflammation is a dominant clinical driver.

Anti-IL-13: Tralokinumab, Lebrikizumab, Eblasakimab

IL-13 is a pleiotropic T2 cytokine central to the pathogenesis of asthma and other eosinophilic disorders.[143] Primarily produced by Th2 lymphocytes, IL-13 acts on structural airway cells, including epithelial cells, ASM, and fibroblasts. It drives key pathological processes such as goblet cell metaplasia and mucus hypersecretion, AHR, subepithelial fibrosis through collagen type I production, and tissue remodeling mediated by matrix metalloproteinase-2 and the transforming growth factor-β1 pathway.[144] Preclinical and translational studies have demonstrated that IL-13 upregulates MUC5AC and promotes goblet cell differentiation, contributing to the mucus-rich phenotype associated with airway plugging.[145] IL-13 also enhances the expression of adhesion molecules and chemokines, thereby promoting eosinophil recruitment and survival, although without directly activating eosinophil effector functions.[146] Elevated IL-13 levels are linked to more severe disease, persistent airway obstruction, and poor asthma control.[147]

Despite the compelling mechanistic rationale, clinical trials of IL-13-targeted mAbs, notably tralokinumab and lebrikizumab, have shown modest efficacy in unselected asthma populations.[143] Tralokinumab, a fully human IgG4 mAb, binds directly to IL-13 and blocks its interaction with both IL-13Rα1 and IL-13Rα2 receptor subunits. Inhibition of binding to both receptors it neutralizes the biological activity of IL-13, including signaling through the IL-4Rα/IL-13Rα1 complex and the decoy receptor IL-13Rα2. Lebrikizumab is a humanized IgG4 mAb that also targets IL-13, but with greater selectivity: it inhibits the formation of the IL-4Rα/IL-13Rα1 heterodimer signaling complex while preserving the binding of IL-13 to IL-13Rα2. This allows continued natural clearance of excess IL-13 via the decoy receptor.[143] Eblasakimab is a first-in-class mAb that selectively targets IL-13Rα1. This blocks downstream STAT6 phosphorylation and suppresses T2 signaling. Early-phase studies in healthy volunteers demonstrated effective STAT6 inhibition following the administration of single doses of 3 mg/kg intravenously or 300 mg subcutaneously, with no serious adverse events reported.[148]

Although biomarker-driven enrichment strategies using periostin, FeNO, or IgE suggest that subgroups may benefit more from IL-13 blockade, these therapies paradoxically reduce FeNO and IgE without consistently lowering exacerbation rates.[149] Currently, no RCTs or guideline recommendations support the use of IL-13 inhibition in COPD.

Phenotype-directed selection is critical when considering IL-13 inhibition for ACO. Only patients with a T2-high, eosinophilic endotype, reflected by elevated blood eosinophils, FeNO, periostin, or sputum IL-13, respond to treatment, whereas T2-low or non-eosinophilic patients generally do not respond.[150] This precision-medicine approach mirrors asthma, where the therapeutic efficacy of biologics is largely restricted to biomarker-enriched populations.

The pathogenic relevance of IL-13 in ACO arises from its multifaceted impact on airflow obstruction. IL-13 alters ASM biology, reducing contractile homeostasis and promoting AHR.[151] It also promotes goblet-cell metaplasia and

Table 3 Future Directions for Biologics in ACO

Research Area	Rationale	Proposed Approach
ACO-specific RCTs	Current trials exclude or underrepresent ACO patients	Dedicated, stratified clinical trials across T2-high, neutrophilic, and mixed endotypes
Biomarker-guided selection	Enhances precision and response prediction	Incorporate eosinophils, FeNO, periostin, IL-33, IL-17, neutrophil markers
Dual-target strategies	Address overlapping cascades (T2 and non-T2)	Comparative studies of IL-33/TSLP vs single-target biologics
Novel endpoints	Traditional COPD/asthma outcomes may miss benefits	Include mucus biomarkers, airway remodeling indices, exacerbation phenotyping, PROs
Real-world evidence	Clinical trials may not reflect practice	Longitudinal registries assessing safety, adherence, and cost-effectiveness
Omics-based discovery	Better characterization of ACO heterogeneity	Multi-omics integration to identify novel targets and refine endotypes

Abbreviations: FeNO, fractional exhaled nitric oxide; IL, interleukin; PRO, patient-reported outcome; RCT, randomized controlled trial; TSLP, thymic stromal lymphopoietin; T2, type 2 inflammation.

MUC5AC overexpression, resulting in excessive mucus hypersecretion and airway plugging. Furthermore, IL-13 amplifies structural remodeling through subepithelial fibrosis and extracellular matrix turnover.[152] Together, these processes suggest that IL-13 plays a central role in airflow limitation and symptom persistence in the T2-high ACO phenotype.

Overall, IL-13 blockade in ACO appears most promising in rigorously defined T2-high subgroups, where mucus hypersecretion and AHR are prominent. However, due to the heterogeneity of ACO, IL-13 inhibition is unlikely to serve as a universal therapy. Rather, it should be viewed as a complementary strategy alongside broader-acting biologics. Future trials should prioritize biomarker-based enrichment and mucus-specific endpoints to clarify the clinical utility of IL-13-targeted therapies.[153]

Conclusion

The ACO population is clinically and biologically heterogeneous, characterized by mixed eosinophilic and neutrophilic inflammation, variable airflow obstruction, and an elevated risk of exacerbations.[6] Biologic therapies targeting T2 pathways, including anti-IL-5, anti-IL-4Rα, anti-IgE, and anti-TSLP agents, show promise, particularly for patients with eosinophilic or T2-high phenotypes. While these therapies reduce exacerbations and corticosteroid dependence in asthma[1] and COPD,[2] evidence specific to ACO remains limited, and no biologic agent has yet been approved or optimized for this population.

Interpretation of current evidence is challenging due to heterogeneity in ACO definitions, inconsistent eosinophil and FeNO thresholds, inclusion of mixed asthma-COPD populations, and variability in study design, endpoints, and follow-up duration. Additional confounding factors, such as smoking status, baseline lung function, prior exacerbations, and concomitant corticosteroid use, further complicate drawing definitive conclusions.

A major strength of this review is its comprehensive synthesis of biologic therapies across asthma, COPD, and ACO. It highlights the importance of biomarkers such as eosinophils, IgE, and FeNO in guiding patient selection. By integrating mechanisms, clinical evidence, and practical implications, and by identifying emerging targets and gaps in ACO-specific trials, this review provides a structured framework for interpreting current data and informing future research. Notably, new strategies, including bispecific antibodies and biologics targeting upstream pathways, are under development, offering potential avenues for broader immunomodulation in overlapping inflammatory profiles.

Future research should focus on rigorously designed, ACO-specific studies with biomarker-guided patient stratification, clinically meaningful endpoints (eg, exacerbation phenotypes, airway remodeling, and health status), and real-world effectiveness assessments (Table 3). Addressing these challenges is essential for optimizing patient selection, clarifying therapeutic efficacy, and integrating biologics into evidence-based treatment strategies for this complex population.

Data Sharing Statement

No datasets were generated or analyzed during the current study.

Author Contributions

Mario Cazzola: Writing – original draft, Conceptualization. Maria Gabriella Matera: Writing – original draft, Validation. Nicola A. Hanania: Writing – review & editing, Validation. Paola Rogliani: Writing – review & editing, Validation. All authors gave final approval of the version to be published, agreed on the journal to which this paper was submitted, and agree to be accountable for the contents of this paper.

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