Ann Allergy Asthma Immunol 123 (2019) 335–344

Contents lists available at ScienceDirect

CME review

Management of asthma COPD overlap

Diego Jose Maselli, MD [*]; Nicola Alexander Hanania, MD, MS [†]

[*] Division of Pulmonary Diseases & Critical Care Medicine, Department of Medicine, University of Texas Health at San Antonio, San Antonio, Texas
[†] Section of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, Baylor College of Medicine, Houston, Texas

Key Messages

- Asthma-COPD Overlap (ACO) is not a distinct disease entity but a term applied to patients with clinical features of both asthma and COPD.
- Asthma-COPD Overlap is associated with greater morbidity than asthma and COPD alone and with relative treatment refractoriness, but information is sparse about its course and optimal treatment.
- Current treatment recommendations are based on consensus because most clinical studies in asthma and COPD have excluded patients with ACO.
- Initial management approach should include addressing environmental triggers as well as identifying and treating underlying comorbidities.
- In selecting pharmacologic therapies, patients with ACO should be treated early with an ICS and 1 or more long-acting bronchodilator.
- In patients with severe disease, every effort should be made to address and target the patient's treatable traits.
- A better understanding of the molecular mechanisms and drivers of airway inflammation in patients with ACO as well as the identification of novel biomarkers may lead to a more precise treatment approach for important unmet needs.

ARTICLE INFO

Article history:
Received for publication July 13, 2019.
Received in revised form July 21, 2019.
Accepted for publication July 21, 2019.

ABSTRACT

Objective: To review the latest literature on management approaches to patients with asthma chronic obstructive pulmonary disease (COPD) overlap (ACO).
Data Sources: Studies and reports were identified from the databases of PubMed/Medline and ClinicalTrials.gov from the US National Institutes of Health and the Cochrane Register of Controlled Trials.
Study Selections: Studies on the management of asthma, COPD, and ACO were included in this review.
Results: Patients with asthma COPD overlap tend to have greater morbidity than those with asthma or COPD alone, but the information on the best therapeutic approach to this group of patients is still limited. Current treatment recommendations rely on expert opinions, roundtable discussions, and strategy documents, because most clinical studies in asthma and COPD have excluded patients with ACO. Because of the potential risk described in patients with asthma with the use of long-acting 2 agonist monotherapy, initial therapy for patients with ACO is recommended to include a long-acting bronchodilator in conjunction with inhaled corticosteroids. Long-acting muscarinic antagonists are effective in both asthma and COPD and should be considered in ACO as an add-on treatment. If inhaler therapy is not effective, advanced therapies based on phenotyping and identification of treatable traits may be considered.
Conclusion: Few studies have evaluated prospectively therapies in the ACO population, and future studies need to determine best strategies for the treatment of these patients, focusing on targeting its different phenotypes and its treatable traits.

Reprints: Nicola A. Hanania, MD, MS, Baylor College of Medicine, 1504 Taub Loop, Houston, TX 77030; E-mail: hanania@bcm.edu.
Disclosures: Dr. Maselli reports consulting fees for GlaxoSmithKline, Sunovion, Sanofi/Regeneron, AztraZeneca and Novartis.
Dr. Hanania reports consulting fees for GSK, Astra Zeneca, Sanofi, Regeneron, Roche, Boehringer Ingelheim, and Novartis; and has received research support from Boehringer Ingelheim, GlaxoSmithKline, and AstraZeneca.
Funding Sources: none.

https://doi.org/10.1016/j.anai.2019.07.021

Instructions

Credit can now be obtained, free for a limited time, by reading the review article and completing all activity components. Please note the instructions listed below:

- Review the target audience, learning objectives and all disclosures.
- Complete the pre-test.
- Read the article and reflect on all content as to how it may be applicable to your practice.
- Complete the post-test/evaluation and claim credit earned. At this time, physicians will have earned up to 1.0 *AMA PRA Category 1 Credit™*. Minimum passing score on the post-test is 70%.

Overall Purpose

Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Describe strategies for diagnosis and management of patients with asthma COPD overlap (ACO).
- Recognize the morbidity and mortality risks for ACO patients, specific therapeutic approaches, expected outcomes and future opportunities for this patient population.

Release Date: October 1, 2019

Expiration Date: September 30, 2021

Target Audience

Physicians involved in providing patient care in the field of allergy/asthma/immunology

Accreditation

The American College of Allergy, Asthma & Immunology (ACAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Designation

The American College of Allergy, Asthma & Immunology (ACAAI) designates this journal-based CME activity for a maximum of 1.0 *AMA PRA Category 1 Credit™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Disclosure Policy

As required by the Accreditation Council for Continuing Medical Education (ACCME) and in accordance with the American College of Allergy, Asthma and Immunology (ACAAI) policy, all CME planners, presenters, moderators, authors, reviewers, and other individuals in a position to control and/or influence the content of an activity must disclose all relevant financial relationships with any commercial interest that have occurred within the past 12 months. All identified conflicts of interest must be resolved, and the educational content thoroughly vetted for fair balance, scientific objectivity, and appropriateness of patient care recommendations. It is required that disclosure be provided to the learners prior to the start of the activity. Individuals with no relevant financial relationships must also inform the learners that no relevant financial relationships exist. Learners must also be informed when off-label, experimental/investigational uses of drugs or devices are discussed in an educational activity or included in related materials. Disclosure in no way implies that the information presented is biased or of lesser quality. It is incumbent upon course participants to be aware of these factors in interpreting the program contents and evaluating recommendations. Moreover, expressed views do not necessarily reflect the opinions of ACAAI.

Disclosure of Relevant Financial Relationships

All identified conflicts of interest have been resolved. Any unapproved/investigative uses of therapeutic agents/devices discussed are appropriately noted.

Planning Committee

- Larry Borish, MD, Consultant, Fees/Contracted Research: AstraZeneca, Novartis, Regeneron, Teva
- Mariana C. Castells, MD, PhD, has no relevant financial relationships to disclose
- Anne K. Ellis, MD, MSc, Advisory Board/Speaker, Honorarium: Alk-Abello, Aralez, AstraZeneca, Boehringer Ingelheim, Circassia Ltd., GlaxoSmithKline, Meda, Merck, Novartis, Pediapharma, Pfizer, Sanofi, Takeda; Research, Grants: Bayer, Circassia Ltd., Green Cross Pharmaceuticals, GlaxoSmithKline, Merck, Novartis, Pfizer, Sanofi, Sun Pharma
- Mitchell Grayson, MD, Advisory Board, Honorarium: AstraZeneca, Genentech, Novartis
- Matthew Greenhawt, MD, Advisory Board/Consultant/Speaker, Fees/Honorarium: Allergenis, Aquestive, DVB Technologies, Genentech, Intrommune, Kaleo, Nutricia, Sanofi/Genzyme
- William Johnson, MD, has no relevant financial relationships to disclosure
- Donald Leung, MD, Chair, DSMC/ Consultant, Fees: AbbVie, Aimmune, Regeneron, Sanofi-Aventis Pharma; Research, Grants: Incyte Corp, Pfizer
- Jay Lieberman, MD, Advisory Board/Author/Speaker, Honorarium/Contracted Research: Aimmune, ALK-Abello, Aquestive Therapeutics, DBV Technologies
- Gailen D. Marshall, Jr, MD, PhD, has no relevant financial relationships to disclose
- Anna Nowak-Wegrzyn, MD, Chair, Honorarium/Contracted Research: Alk-Abello, Merck; Consultant, Fees: LabCorp; Co-Investigator, Fees: Sanofi Aventis; Private Investigator, Contracted Research/Honorarium: Abbott, Astellas Pharma, Danone Nutricia, DBV Technologies, Nestle
- John J. Oppenheimer, MD, Consultant, Fees: DBV Technologies, GlaxoSmithKline, Sanofi, Teva; Adjudication, Fees: MedImmune
- Jonathan M. Spergel, MD, PhD, Advisory Board/Consultant/Research, Fees/Contracted Research/Honorarium: Aimmune Therapeutics, DBV Technologies, Regeneron, Pfizer; Speaker, Honorarium: Abbott

Author

The following individual has no relevant financial relationships to disclose:

- Gailen D. Marshall, Jr., MD, PhD

Recognition of Commercial Support: This activity has not received external commercial support.

CME Inquiries: Contact the American College of Allergy, Asthma & Immunology at education@acaai.org or 847-427-1200.

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are the most common chronic pulmonary conditions. Both diseases have considerable heterogeneity but share a substantial number of clinical features. Over the past decade, significant interest has been expressed in the group of patients who have overlapping characteristics of both diseases. Although previously described as asthma COPD overlap syndrome (ACOS), the terminology of "syndrome" has now been abandoned because it does not describe a separate disease entity, but rather a spectrum of overlapping features of both asthma and COPD. Asthma COPD overlap (ACO) is a term now used to refer to this spectrum of chronic airways disease. However, much controversy exists about the exact definition of ACO between studies, and therefore its exact prevalence among the asthma and COPD populations is difficult to estimate. In general, using the various definitions, most studies suggest that the prevalence of ACO ranges between 1.1% and 4.5% in the general population but is considerably higher in asthma and COPD populations, with a reported prevalence of 27% and 33%, respectively.[1–4]

As previously mentioned, several definitions for ACO have been proposed, but no consensus exists. These definitions include the need for documentation of fixed airway obstruction depicted by a post-bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio of less than 0.7 in the setting of clinical features that include age older than 40 years, significant history of smoking or other known exposure, patient-reported or a physician's diagnosis of asthma, significant bronchodilator reversibility in FEV_1 of more than 200 to 400 mL, the presence of significant sputum or blood eosinophilia, and documentation of wheezing or an atopic disease.[5–9] Irrespective of the definition for ACO, most studies suggest that these patients have worse outcomes than patients with either disease. For example, patients with ACO have more respiratory symptoms, worse quality of life, greater physical impairment, and higher risk of exacerbations, cost of care, and more health care utilization.[2,5,10–12] The reasons for why the course of the disease in these patients tends to be associated with worse outcomes than those of patients with either asthma or COPD are not well understood. However, possibly triggers for its exacerbations are broader, or patients with ACO may inherently be more susceptible for the progression of their disease.

Initial Evaluation of Patients with ACO

In a joint statement by the Global Initiate for Asthma (GINA) and Global Initiate for Chronic Obstructive Lung Disease (GOLD), several steps have been proposed for the evaluation of patients with suspected ACO.[13] The first step is to confirm the accurate diagnosis of the patient. This includes a complete clinical history evaluating chronic symptoms such as cough, sputum production, dyspnea, recurrent respiratory infections, and exposures to environmental hazards, tobacco exposure, prior diagnoses of asthma or COPD, and prior response to inhaler therapy. Physical examination is also key and may reveal features of hyperinflation, wheezing, and other abnormalities. Radiographic testing also may aid in the diagnosis or confirmation of the disease. Computed tomography may indicate emphysema or other abnormalities that can guide therapy. The second step involves evaluating features that may favor the diagnosis of asthma or of COPD (Table 1). Patients with ACO have overlapping features of both diseases. The third step includes the evaluation physiologic measures, including spirometry (Table 2). These steps are crucial to determine whether a patient has ACO and are imperative in selecting appropriate therapy, particularly in more severe disease, in which the therapies of asthma and COPD diverge.

Pharmacologic Therapy in ACO

Because of heterogeneity of ACO and lack of consensus on its definitions, therapy of this disease is based on treating both the underlying asthma and COPD. Furthermore, patients with ACO have notoriously been excluded from clinical trials evaluating asthma and COPD therapies, and lack of solid clinical evidence makes it difficult to determine appropriate treatment strategies. In addition, some patients may present with features of both asthma and COPD in equipoise, and the distinction may be problematic, especially in asthma patients who smoke, older patients with asthma, and COPD patients who have underlying type 2 (T2) airway inflammation reflected by sputum or blood eosinophilia.

Pharmacologic Treatment Mild/Moderate ACO

Initial management of patients with ACO should adopt a similar approach to that used in patients with asthma or COPD. Every effort has to be made to identify triggers and limit the patient's exposures. Smoking cessation is particularly important in patients with ACO, because this irritant will affect the progression and symptoms control in asthma and COPD independently. In addition, smoke exposure has been shown to decrease the response to inhaled corticosteroids.[14] Evaluation of other exposures such as biomass smoke, pollution, and other irritants needs to be considered. Delivering patient education and ensuring adequate inhaler technique are vital in this group of patients and should be encouraged at every visit.[15,16] Using an active management cycle in which patients are assessed, the response is reviewed, and the treatment is adjusted based on their symptoms and exacerbation history is also recommended.[15,16] When selecting therapies, identifying underlying comorbidities is key, because increasing evidence shows that

Table 1
Clinical Features Outlining the Differences and Similarities of Asthma and COPD[13]

Feature	Favors asthma	Favors COPD
Age of onset of symptoms	Before age 20 years	After age 40 years
Features of respiratory symptoms	Triggered by allergens, exercise, humidity, variations in temperature	Chronic symptoms despite therapy: cough, sputum production
	Day-to-day variability	Exertional dyspnea
Lung function	Variable airflow limitation	Airflow limitation with a fixed post-bronchodilator $FEV_1/FVC < 0.70$
	Reversibility	
History	Previous diagnosis of asthma	Previous diagnosis of COPD
	Family history of asthma and atopic conditions	Significant exposure to tobacco smoke or other noxious agent
Variability over time	Seasonal variability	Slow progression of symptoms
Response to therapy	Spontaneous improvement	Bronchodilators provide limited relief
	Rapid improvement to bronchodilators and gradual response to ICS	
Radiographic findings	Chest X-ray: may be normal	Chest X-ray: hyperinflation
	Chest CT: may show airway thickening and mosaicism	Chest CT: emphysema

COPD, chronic obstructive pulmonary disease; CT, computed tomography; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 2
Spirometric Changes in Asthma, COPD, and ACO[13]

Spirometric measure	Asthma	COPD	ACO
Normal post bronchodilator FEV_1/FVC	Consistent with the diagnosis	Not consistent with the diagnosis	Not consistent with the diagnosis
Post-bronchodilator $FEV_1/FVC < 0.70$	Consistent with airflow limitation but may respond to treatment	Required for the diagnosis	Consistent with the diagnosis
Post-bronchodilator $FEV_1 > 80\%$ predicted	Consistent with the diagnosis with good asthma control	Mild disease if post bronchodilator $FEV_1/FVC < 0.70$	Consistent with the diagnosis if post bronchodilator $FEV_1/FVC < 0.70$
Post-bronchodilator $FEV_1 < 80\%$ predicted	Consistent with the diagnosis with increased risk of asthma exacerbations	FEV_1 used for severity assessment and may indicate risk factors (ie, mortality)	FEV_1 used for severity assessment and may indicate risk factors (ie, mortality)
Post-bronchodilator increase of $FEV_1 > 12\%$ and 200 mL	Commonly encountered	Occasionally encountered	Occasionally encountered
Post-bronchodilator increase of $FEV_1 > 12\%$ and 400 mL	High probability of asthma	Infrequently encountered	Consistent with the diagnosis

ACO, asthma COPD overlap; COPD, chronic obstructive pulmonary disease; CT, computed tomography; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

comorbid conditions may exert a considerable effect in patients with ACO, and considering diagnoses such as gastroesophageal reflux disease, osteoporosis, cardiovascular disease, and depression is essential.[17]

Therapy for mild to moderate disease in patients with chronic airway disease, including asthma and COPD, is centered on inhaled therapy (Fig 1). Patients with asthma or COPD are treated in a stepwise approach based on symptom control and history of exacerbations.[15,16] Patients with infrequent symptoms can be managed with as-needed short-acting bronchodilators. Nevertheless, as the symptoms progress, the treatment of asthma and COPD differ. Specifically, in the introduction of inhaled corticosteroids (ICS), patients with asthma are introduced in the earlier stages, whereas in COPD they are limited to patients with a history of exacerbations not responding to long-acting bronchodilators. In asthma, early introduction of ICS can decrease the risk of exacerbations and improve asthma control.[18,19] Long-acting $\beta 2$ agonists (LABA) are recommended as an add-on therapy if other controllers are not effective.[16] Single therapy with a LABA in asthma is contraindicated because in 2 trials, salmeterol was linked to increased risk of asthma-related death.[20,21] Conversely, in COPD, the use of long-acting bronchodilators, LABAs, or long-acting muscarinic antagonists (LAMA) has been associated with improvements in symptoms, quality of life, lung function, and exacerbation risk.[22–25]

Although limited evidence is available on the initial approach to inhaler therapy in patients with ACO, avoiding single therapy with LABA is judicious in this group of patients because of the safety concerns observed in the asthma population.[13] Therefore, the early use of ICS in this population has been recommended to target airway inflammation, but because these patients have concomitant airway obstruction, managing their symptoms should include adding 1 or more long-acting bronchodilators, often with the initial addition of a LABA. The early use of ICS in combination with a LABA in treatment for patients with COPD who have a history of asthma is supported by a case-control study.[26] Gershon and colleagues[26] evaluated data from older adults with COPD, particularly those with concomitant asthma (ie, ACO), and they demonstrated that newly prescribed LABA/ICS therapy, compared with newly prescribed LABAs alone, was associated with a significantly lower risk of the composite outcome of death or COPD hospitalization.[26] Although commonly used, a great need remains to better understand the role of the long-term efficacy and safety of inhaled corticosteroids in the ACO population. Indeed, prospective clinical trials are required to validate (or refute) response to ICS and the

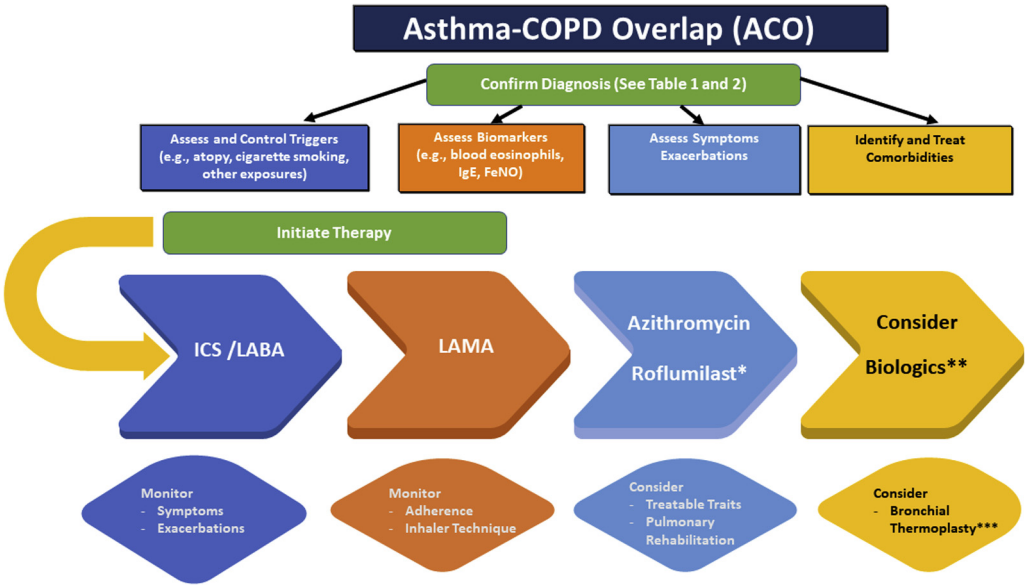

Figure 1. Approach to management of patients with ACO. LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid; FeNO, fractional exhaled nitric oxide; *Consider in severe patients with chronic bronchitis. **Consider in allergic and eosinophilic phenotypes. ***Consider in patients with underlying severe asthma.

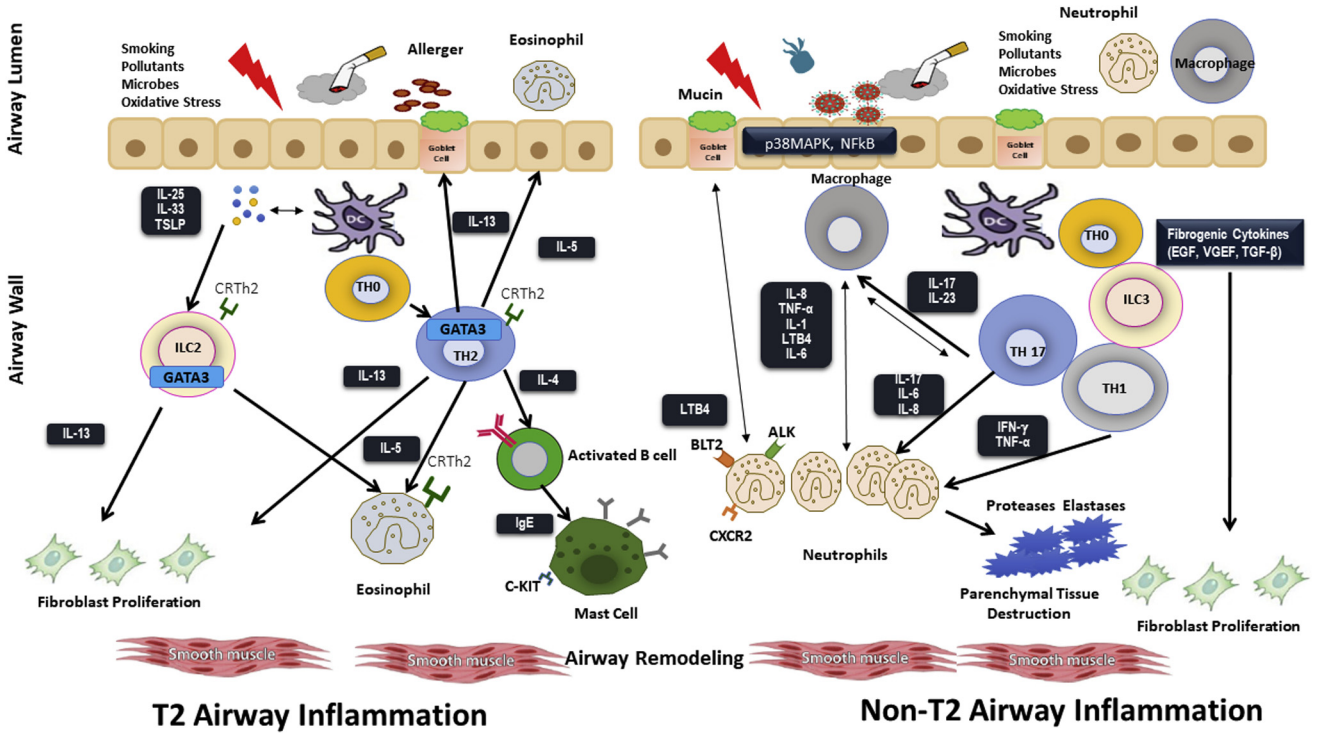

Figure 2. Cellular and molecular targets of airway inflammation in asthma, COPD, and ACO. IL, interleukin; ILC2, type 2 innate lymphoid cell; Th2, T helper 2; TSLP, thymic stromal lymphopoietin; BLT2, leuko triene B4 receptor 2; CXCL8, CXC motif chemokine ligand 8; TFG-β, transforming growth factor β; CXCL, chemokine ligand. Modified from Assaf S, Hanania NA. *Exp Rev Precis Med Drug Dev.* 2019;4:121-128.

cost-effectiveness of this approach. Patients treated with ICS/LABA who continue to have symptoms are often treated with an additional long-acting bronchodilator, such as a LAMA. Tiotropium bromide has been the most commonly used LAMA in this situation, because it is the only one currently approved for treatment of asthma. In a large, 12-week, randomized, double-blind, placebo-controlled, parallel group, clinical trial, Magnussen et al[27] demonstrated that patients with COPD who have concomitant asthma (ACO) achieve spirometric improvements with tiotropium along with symptomatic benefit, as seen by reduced need for rescue medication.[27] Triple inhaler therapy (ICS/LABA/LAMA) has been effective in both asthma and COPD and therefore should be considered if the patient's symptoms progress, especially if there is a history of frequent exacerbations.[28–30] If inhaler therapy is not effective in these patients, advanced therapies based on phenotyping and identification of treatable traits may be considered. These include the use of monoclonal antibodies, phosphodiesterase inhibitors, and macrolides (Fig 1).

Pharmacologic Treatment of Severe ACO

Biologics

Understanding the molecular mechanisms of airway inflammation in both asthma and COPD has led to the identification of novel targets for therapy that include cytokines and chemokines (Fig 2). Indeed, several monoclonal antibody biologics and small molecule inhibitors and antagonists have been developed and are either approved or currently being evaluated in clinical trials. Monoclonal antibodies targeting T2 inflammation in severe asthma have thus far been the most successful, and 5 different monoclonal antibodies are now approved for the treatment of severe T2 high asthma (allergic and eosinophilic asthma); others are being evaluated (Fig 3). Biomarkers, such as immunoglobulin E (IgE) and peripheral blood eosinophils, and exhaled nitric oxide (FeNO) can identify patients who may benefit from these therapies.[31–36] The use of these therapies has been associated with significant reduction in exacerbations, emergency room visits, need for systemic corticosteroids, and improvements in quality of life, among other outcomes.[31–40]

Because of the success of biologics in asthma, a similar strategy has been attempted in patients with COPD whose phenotypic characteristics that may predict a favorable response, such as those with underlying T2 airway inflammation and eosinophilic features. However, the results of these studies have shown mixed results. For example, a randomized, double-blinded, placebo-controlled study explored the effects of benralizumab, a monoclonal antibody targeting the alpha subunit of the interleukin (IL)-5 receptor, in 101 patients with COPD and at least 3% sputum eosinophil count and at least 1 exacerbation in the previous 12 months.[41] Treatment with benralizumab for 56 weeks was associated with significant eosinophil count reductions, but not with reductions in the annualized rate of exacerbations compared with placebo, 0.95 (0.68-1.29) vs 0.92 (0.67-1.25), respectively. No difference was seen in the severe exacerbations leading to a hospitalization or health care–related quality of life. Interestingly, improvement of pre-bronchodilator FEV_1 occurred in the treatment group at week 56 compared with placebo (130 mL $\pm$ 410 vs -60 mL $\pm$ 240, $P = .014$). Subgroup analyses suggested that patients with higher peripheral blood eosinophil counts may have benefits, but the study was not powered to accurately determine these differences. Nevertheless, this was the first study to show potential benefits of targeting eosinophilic inflammation in COPD. No safety concerns were reported.

In a pilot study, the effects of mepolizumab, a monoclonal antibody that neutralizes IL-5, were evaluated in 18 COPD patients with at least 1 exacerbation in the past 12 months and sputum eosinophil counts greater than 3%.[42] Importantly, patients with a previous diagnosis of asthma were not excluded. Patients that were randomized to receive mepolizumab experience reductions in both

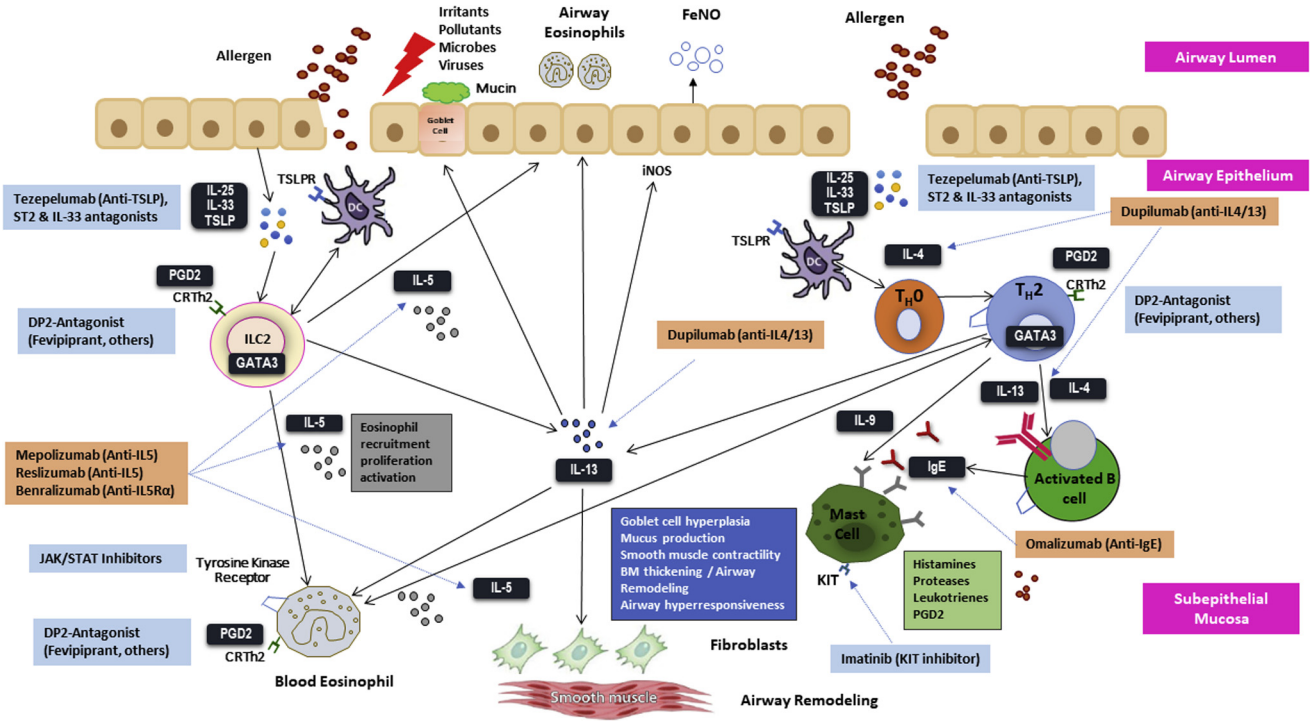

Figure 3. Therapies approved or under development targeting T2 airway inflammation.[105] DC, dendritic cell; ILC2, group 2 innate lymphoid cell; KIT, proto-oncogene c-kit; Th2, T-helper cell; PGD2, prostaglandin D2; TSLP, thymic stromal lymphopoietin; CRTH2, chemoattractant receptor homologous molecule expressed on TH2 cells. Used with permission from: Assaf S, Hanania NA. *Curr Opin Allergy Clin Immunol.* 2019;19:379-386.

sputum and blood eosinophil counts, but they did not have significant improvements in exacerbation rates or lung function compared with placebo. These findings were limited by the size of the trial and the relatively short duration of treatment (6 months). These limitations were overcome in the phase 3 METREX and METREO trials.[43] The patients included in these trials had a diagnosis of COPD confirmed by spirometry, had at least 2 exacerbations or 1 severe exacerbation that led to hospitalization in the prior year, and were receiving background therapy of inhaled corticosteroids in addition to a long-acting bronchodilator. In METREX, 836 patients with and without an eosinophilic phenotype (more than 150 eosinophils per microliter in the peripheral blood) were randomized to receive mepolizumab at 100 mg every 4 weeks of placebo (1:1). In METREO, 675 patients with an eosinophilic phenotype were randomized to receive mepolizumab at 100 mg or 300 mg every 4 weeks or placebo (1:1:1). In both trials, patients received treatment for 52 weeks. In METREX, the mean annualized rate of moderate or severe exacerbations was lower in the in the mepolizumab group compared with placebo (1.4 vs 1.71 per year, relative risk [RR] 0.82; 95% confidence interval [95%CI], 0.68-0.98; $P = .04$). The time to the first exacerbation was longer in the mepolizumab group compared with placebo, 192 vs 141 days, respectively (hazard ratio 0.75; 95%CI, 0.60-0.94, $P = .04$). In METREO, the annualized rates of exacerbations were lower in the mepolizumab groups compared with placebo, but did not reach statistical significance (1.19 in the 100-mg group [RR 0.80; 95%CI, 0.65-0.98, $P = .07$], 1.27 in the 300-mg group [RR 0.86; 95%CI, 0.70-1.05; $P = .14$] vs 1.49 in the placebo group. In both trials, lung function and measures of health-related quality of life were similar. No new safety signals were observed in either trial. The Food and Drug Administration concluded that the magnitude and consistency of the benefits were not sufficient to approve the use of mepolizumab in COPD.[44] Additionally, they expressed the opinion that smokers with a history of asthma should have been excluded at screening to limit underlying asthma as confounder.

Most recently, 2 randomized, double-blind, double-dummy, placebo-controlled, parallel-group, phase 3 studies evaluating the use of benralizumab in moderate to very severe COPD with a history of exacerbations were completed (TERRANOVA and GALATHEA).[45] TERRANOVA was a dose ranging study that evaluated subcutaneous benralizumab every 8 weeks (first 3 doses every 4 weeks) at 3 different doses: 10 mg, 30 mg, and 100 mg compared with placebo. A total of 1545 patients with a baseline eosinophil count greater than 220 cells/μL received therapy or placebo for 56 weeks. No significant improvements were observed in the annual exacerbation rates in the 10-mg (RR 0.85, 95%CI 0.71-1.01, $P = .06$), 30-mg (RR 1.04, 95%CI 0.88-1.23, $P = .66$), or 100-mg (RR 0.93, 95%CI 0.78-1.10, $P = .40$) treatment groups compared with placebo. Similarly, no improvements in lung function or respiratory symptoms were observed. In GALATHEA, 2 doses (30 mg or 100 mg subcutaneously every 8 weeks, with the initial 3 doses every 4 weeks) of benralizumab were evaluated in 1120 patients with moderate to very severe COPD and a blood eosinophil count greater than 220 cells/μL. The patients received either 1 of the benralizumab doses or placebo for 56 weeks or placebo as an add-on therapy to dual- or triple-inhaler therapy. A trend toward improvement in the annual rate of exacerbations was seen with the 30-mg (RR 0.96, 95%CI 0.80-1.15, $P = .65$) and 100-mg (RR 0.83, 95%CI 0.69-1.00, $P = .05$) dosing schemes compared with placebo. Likewise, no significant differences were observed with respect to lung function and respiratory symptoms. Interestingly, patients in the 100-mg dosing group had a significant improvement in the annual rate of severe exacerbations (RR 0.57, 95%CI 0.36-0.91, $P = .02$). In both TERRANOVA and GALATHEA, adverse events were similar in the treatment and placebo groups, and they were consistent with the benralizumab phase 3 trials in severe eosinophilic asthma.[35,36,46] In summary, targeting the IL-5 pathway does not consistently improve outcomes in COPD, even in those with a history of exacerbations and an eosinophilic phenotype. Subgroup analyses have identified potential patient populations who may benefit from

these therapies, particularly those with higher peripheral blood eosinophil counts, but future studies will require larger patient populations. Possibly, just as with asthma, earlier studies will serve as the basis for future studies in which other clinical factors and biomarkers will lead to better identify responders. Reassuringly, the therapies studied to date are safe and well tolerated, but long-term data are still required.

Targeting pathways beyond IL-5 is being considered for future therapies in both asthma and COPD. In asthma, promising results target alarmins released by airway epithelial cells, in particular thymic stromal lymphopoietin (TSLP), IL-25, and IL-33. Targeting these costimulatory cytokines can block T2 inflammatory response and may have important clinical implications. For example, tezepelumab, a monoclonal antibody targeting TSLP, was shown to decrease the rate of exacerbations in patients with uncontrolled moderate-to-severe asthma irrespective of blood eosinophil counts.[47] Murine models have shown that inhibition of IL-25 or IL-33 reduces T2 cytokine production and eosinophilic inflammation, and the results of ongoing human trials are eagerly awaited (NCT03112577).[48,49] In COPD, an ongoing trial (NCT03930732) is evaluating the use of dupilumab, an inhibitor of the alpha subunit of the IL-4 receptor, in patients with moderate to severe COPD. The results of these trials and others will help determine the role of targeting these pathways in COPD.

Only a few studies of biologics have been conducted in ACO. This is possibly attributable to the varying definitions of ACO, wide range of disease severity, and exclusion and inclusion criteria for the different studies. For these reasons, studies are limited to case reports, registries, and real-life experiences.[50–53] Omalizumab has been studied the most in patients with overlapping features. An analysis of 177 subjects from the Australian Xolair Registry indicated similar improvements in health care–related quality of life and asthma control in patients with severe allergic asthma compared with those with COPD overlapping features.[52] No improvements were observed in lung function. The PROSPERO study (Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab) was an observational, real-life study that evaluated the effectiveness of omalizumab after 48 weeks of therapy.[54] Current and prior smokers and patients with coexisting COPD were not excluded from this study. In a post hoc analysis of 737 patients from this cohort (ACO n = 56, non-ACO n = 681), patients with and without overlapping features had similar improvements in exacerbation rates and asthma control.[53] Nevertheless, because of the inherent limitations of a real-life study, these data should be interpreted with caution, because these types of studies have less rigor compared with the regulatory trials previously described.

The question remains as to whether one should use biologics on a routine basis in patients with ACO. Limited data are available to make a definitive recommendation regarding the use of these treatments in patients with overlapping features. In clinical practice, patients with uncontrolled asthma and coexisting COPD are encountered regularly. A real-life study showed that 22% to 30% of patients that receive biologicals for asthma have coexisting COPD.[55] This suggests that these patients are already receiving these therapies routinely. When all clinical management goals have been addressed, such as disease education, environmental measures, smoking cessation, and treatment of comorbid conditions, considering biological therapies in ACO is reasonable. Taking into consideration the robust evidence of improvements in multiple important asthma outcomes and understanding the limited ACO-specific studies, biologics likely should not be withheld in patients with ACO, particularly if patients' conditions remain uncontrolled with frequent exacerbations or on chronic oral corticosteroids. Fortunately, biologics have been considered generally safe in the COPD population, but information of ongoing studies will provide additional safety information.

Targeting non-T2 airway inflammation including neutrophilic inflammation remains a great unmet need for treatment of severe asthma and COPD. Several agents, including biologics such those targeting IL-8, IL-17 and tumor necrosis factor-alpha and small molecule antagonists such as CXCR2 and LTB4 antagonists, have failed to show benefits in clinical trials.[56–61] Several other targets are being evaluated (Fig 2), but none of these has been evaluated in patients with ACO.

The identification of treatable traits remains the recommended approach in patients with ACO.[62–65] These treatable traits should be clinically relevant, be easily identified and measured, and have therapeutic implications.[63] These traits include biomarkers, such as those used for the selection of biologicals in asthma, but they also may include respiratory symptoms, radiographic characteristics, comorbid conditions, history of exacerbations or infections, and others,[65] for example, using the combination of 2 biomarkers, periostin and Chitinase-3-like protein 1 (YKL-40), Shirai and colleagues[66] were able to better characterize 3 populations of patients with chronic airway disease.[66] Patients with asthma and ACO had higher levels of periostin but not in COPD, whereas YKL-40 was high in COPD and ACO but not in asthma.[66] Future studies need to explore ways to ensure more appropriate selection of patients, using clinical traits and biomarkers to identify responders.

Macrolides

Macrolides have been useful in various chronic pulmonary diseases, including diffuse panbronchiolitis, noncystic bronchiectasis, and cystic fibrosis. In asthma and COPD, various trials have been shown to provide benefits regarding exacerbations and other important outcomes. The mechanisms explaining these benefits are incompletely understood. The anti-microbial properties of these compounds may be beneficial in certain cases. Notably, infections with atypical pathogens may contribute to exacerbations, uncontrolled symptoms, and progression of the disease.[67] Additionally, some evidence links toxins from *Mycoplasma pneumoniae* and infection with other atypical bacteria with T2 inflammatory responses and airway remodeling that may be possibly mitigated with macrolides.[67,68] The potential anti-inflammatory properties of macrolides also have been debated considerably, but mounting evidence suggests that this class of medications may affect the various inflammatory pathways. For example, clarithromycin has been linked to suppression of the IL-13–mediated production of mucus by goblet cells and periostin by fibroblasts.[69,70] Various studies also have shown that macrolides may reduce airway reactivity and remodeling.[71–74] Emerging evidence also suggests that these medications may alter gene expression.[75] In relation to ACO, these potential benefits appear to extend to inflammation induced by smoke exposure.[76,77]

Various trials have evaluated the use of macrolides in asthma, with mixed results. A systematic review of 23 studies showed that macrolides were not consistently beneficial compared with placebo in asthma, but evidence was considered to be of low quality because of the considerable heterogeneity of study populations, interventions, and reported biases.[78] Other meta-analyses had similar observations and suggested improvements in quality of life, symptoms scores, and airway hyperreactivity.[79,80] The AMAZES study was a randomized, double-blind, placebo-controlled trial, and the largest to date evaluating the effects of azithromycin in asthma.[81] It included 420 patients with persistent uncontrolled asthma despite ICS/LABA that were treated with azithromycin 500 mg 3 times per week or placebo (1:1) for 48 weeks. Treatment with azithromycin was associated with reduced yearly asthma exacerbations rates compared with placebo (1.07; 95%CI 0.85-1.29 vs 1.86; 95%CI 1.54-2.18, $P < .001$). Improvement was seen as well in

asthma quality of life. Patients with eosinophilic and non-eosinophilic phenotypes experienced similar improvements. Diarrhea was more frequently encountered in the treatment group, but overall azithromycin was well tolerated.

Several clinical trials support the chronic use of azithromycin in COPD. Albert and colleagues[82] demonstrated that daily 250 mg of azithromycin prevented COPD exacerbations compared with placebo after 1 year of therapy in addition to usual care.[82] Although significant improvements in quality of life occurred, a small number of patients experienced hearing problems with therapy. Other studies have supported these findings, even beyond 12 months of therapy.[83–86] More recently, a study showed that azithromycin therapy also may have a role during the highest risk period after acute exacerbation of COPD (AECOPD).[87] In the study by Vermeersch and colleagues,[87] 301 patients were enrolled after an AECOPD and received 3 months of azithromycin or placebo.[87] Patients that received therapy had a lower rate of treatment failure after 3 months compared with placebo (49 vs 60%, HR = 0.73; 95%CI 0.53-1.01, $P = .0526$). Patients in the azithromycin arm also experienced less intensification of the treatment and readmissions. The clinical benefits were lost after 6 months of therapy. This suggest that in at-risk patients, longer courses of therapy may be required.

No study has evaluated prospectively the effects of macrolides in patients with ACO, and few data on the use of macrolides in ACO exist. In a study that evaluated the use of low-dose azithromycin in patients with primary antibody deficiency, both asthma and COPD were enrolled in addition to other chronic lung diseases. Similar to these studies, exacerbation reductions were observed in these at-risk populations.[88] Given the evidence from studies in both asthma and COPD populations, azithromycin can be considered as an adjunctive therapy in patients with ACO. However, this therapy should be reserved for patients whose condition remain uncontrolled despite ICS/LABA, those whose condition has failed to respond to other therapies, or those considered at-risk for future exacerbations. Long-term azithromycin use has been linked to increased antimicrobial resistance, and a careful risk/benefit evaluation should be done before initiating this therapy.[81,89] Prescreening patients for the risk of cardiac arrhythmias and hearing problems and close post-initiation monitoring is recommended if the decision to start azithromycin is made.[90]

Phosphodiesterase inhibitors

Theophylline, a nonselective phosphodiesterase inhibitor, was 1 of the first medications used in treatment of patients with chronic airways diseases, and in fact, is still used worldwide in milder forms of asthma and COPD.[15,16,91] In COPD, theophylline has been shown to improve lung function and symptoms, but it does not reduce the rate of exacerbations.[92,93] Similarly, in patients with asthma, improvements in lung function were seen after treatment with theophylline, but no changes in the control of the disease.[94,95] Doxofylline, another methylxanthine, has similar benefits in asthma compared with theophylline, but it may have a safer profile.[96,97] To date, no studies have been conducted evaluating the efficacy of methylxanthines in an ACO population. In patients that have milder forms of ACO, this class of medications may be considered, but other safer and more effective therapies exist.

The oral phosphodiesterase-4 inhibitor roflumilast has been effective in improving lung function and decreased exacerbations rates in a subgroup of patients with COPD—those with a history of frequent exacerbations, a chronic bronchitis phenotype, and a FEV_1 less than 50% predicted.[98–100] In asthma, roflumilast has shown consistent improvements of lung function in a meta-analysis of 14 trials.[101] Moreover, roflumilast is generally well-tolerated in asthma, and the most frequently reported side effects include diarrhea, nausea, and headache.[101,102] No data exist on the effects of roflumilast in ACO patients. Interestingly, COPD patients with higher counts of eosinophils had greater reduction in exacerbation rates.[103] Supporting these findings, a study of bronchial biopsies of COPD patients indicated a decrease in tissue eosinophils after 16 weeks of therapy with roflumilast compared with placebo.[104] Other studies have shown anti-inflammatory effects mediated by other cellular lines, such as neutrophils.[105] The findings on the studies in asthma and COPD, and the potential effects on eosinophils and other anti-inflammatory properties, makes roflumilast an attractive option to examine further in patients who have ACO who are at risk of frequent exacerbations.

Nonpharmacologic Management of ACO

Other management approaches for ACO include nonpharmacologic strategies. All patients should engage in regular physical activity and pursue a healthy diet.[15,16] Weight loss has been shown to be beneficial in asthma and is recommended in the setting of obesity.[106] Avoidance of known triggers, including occupational and indoor exposures, remains very important.[16] Aspirin and other nonsteroidal anti-inflammatory drugs can worsen asthma control; thus, caution should be exercised in all patients with features of asthma.[107] Pneumococcal vaccination is recommended for patients older than 65 years; in COPD it has been shown to reduce the likelihood of exacerbations.[108] Annual influenza vaccination has been beneficial in both asthma and COPD and should be advocated in ACO patients.[109,110] Pulmonary rehabilitation has been found to be effective in a wide range of severities in symptomatic patients with COPD and should be offered also to patients with ACO.[111] Bronchial thermoplasty has only been studied in severe asthma, and its effects on ACO patients remain unknown.[112] Although most of these nonpharmacological measures have not been evaluated in the ACO population, their efficacy has been demonstrated independently in COPD and in asthma, and they should be contemplated in all patients with features of both diseases.[13,15,16]

Conclusion

Asthma-COPD overlap is not a distinct disease entity but a term applied to patients with clinical features of both asthma and COPD. Epidemiologic studies suggest that ACO is associated with greater morbidity than asthma and COPD alone, and with relative treatment refractoriness, but information is sparse about its course because most clinical studies have excluded such patients. Therefore, current recommendations for therapy are based on expert opinion, roundtable discussions, and strategy documents (ie, GINA and GOLD), and they suggest that initial therapy of patients with ACO should include 1 or more long-acting bronchodilators, the cornerstone of COPD treatment and an inhaled corticosteroid, the cornerstone of asthma treatment. In severe disease, management should target treatable traits as well as be driven by phenotypic and endotypic characterization of the patients. Several biologic therapies are now available that target drivers of T2 airway inflammation in asthma, but few of these have thus far been evaluated in the ACO population. Targeting non-T2 inflammation remains a major unmet need. In the future, a better and more in-depth understanding of the molecular mechanisms of ACO and its related phenotypes will help identify future targets of therapy.

References

1. Wurst KE, Kelly-Reif K, Bushnell GA, Pascoe S, Barnes N. Understanding asthma-chronic obstructive pulmonary disease overlap syndrome. *Respir Med*. 2016;110:1–11.
2. de Marco R, Pesce G, Marcon A, et al. The coexistence of asthma and chronic obstructive pulmonary disease (COPD): prevalence and risk factors in young, middle-aged and elderly people from the general population. *PLoS One*. 2013; 8(5):e62985.

3. Kumbhare S, Pleasants R, Ohar JA, Strange C. Characteristics and prevalence of asthma/chronic obstructive pulmonary disease overlap in the United States. *Ann Am Thorac Soc*. 2016;13(6):803–810.
4. Mendy A, Forno E, Niyonsenga T, Carnahan R, Gasana J. Prevalence and features of asthma-COPD overlap in the United States 2007-2012. *Clin Respir J*. 2018;12:2369–2377.
5. Hardin M, Silverman EK, Barr RG, et al. The clinical features of the overlap between COPD and asthma. *Respir Res*. 2011;12:127.
6. Hardin M, Cho M, McDonald ML, et al. The clinical and genetic features of COPD-asthma overlap syndrome. *Eur Respir J*. 2014;44:341–350.
7. Tashkin DP, Chipps BE, Trudo F, Zangrilli JG. Fixed airflow obstruction in asthma: a descriptive study of patient profiles and effect on treatment responses. *J Asthma*. 2014;51:603–609.
8. Sin DD, Miravitlles M, Mannino DM, et al. What is asthma-COPD overlap syndrome? Towards a consensus definition from a round table discussion. *Eur Respir J*. 2016;48:664–673.
9. Cosentino J, Zhao H, Hardin M, et al. Analysis of asthma-chronic obstructive pulmonary disease overlap syndrome defined on the basis of bronchodilator response and degree of emphysema. *Ann Am Thorac Soc*. 2016;13:1483–1489.
10. Menezes AMB, Montes de Oca M, Pérez-Padilla R, et al. Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype: COPD-asthma. *Chest*. 2014;145:297–304.
11. Diaz-Guzman E, Khosravi M, Mannino DM. Asthma, chronic obstructive pulmonary disease, and mortality in the U.S. population. *COPD*. 2011;8:400–407.
12. Alshabanat A, Zafari Z, Albanyan O, Dairi M, FitzGerald JM. Asthma and COPD overlap syndrome (ACOS): a systematic review and meta analysis. *PLoS One*. 2015;10:e0136065.
13. Global Initiative for Asthma and Global Initiative for Chronic Obstructive Pulmonary Disease. Diagnosis and initial treatment of asthma, COPD, and asthma-COPD overlap. http://ginasthma.org/download/824/. Accessed July 1, 2019.
14. Lazarus SC, Chinchilli VM, Rollings NJ, et al. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. *Am J Respir Crit Care Med*. 2007;175:783–790.
15. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease, 2019 update https://goldcopd.org/gold-reports/. Accessed July 1, 2019.
16. Global Initiative for Asthma. Global strategy for asthma management and prevention, 2019 update https://ginasthma.org/gina-reports/. Accessed July 1, 2019.
17. Maselli DJ, Hanania NA. Asthma COPD overlap: impact of associated comorbidities. *Pulm Pharmacol Ther*. 2018;52:27–31.
18. Pauwels RA, Pedersen S, Busse WW, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet*. 2003;36:1071–1076.
19. Busse WW, Pedersen S, Pauwels RA, et al. The inhaled steroid treatment as regular therapy in early asthma (START) study 5-year follow-up: effectiveness of early intervention with budesonide in mild persistent asthma. *J Allergy Clin Immunol*. 2008;121:1167–1174.
20. Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ*. 1993;306:1034–1037.
21. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest*. 2006;129:15–26.
22. Kew KM, Mavergames C, Walters JA. Long-acting beta2-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2013;(10):CD010177.
23. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359:1543–1554.
24. Wise RA, Anzueto A, Cotton D, et al. Tiotropium Respimat inhaler and the risk of death in COPD. *N Engl J Med*. 2013;369:1491–1501.
25. Kerstjens HA, Engel M, Dahl R, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med*. 2012;367:1198–1207.
26. Gershon AS, Campitelli MA, Croxford R, et al. Combination long-acting β-agonists and inhaled corticosteroids compared with long-acting β-agonists alone in older adults with chronic obstructive pulmonary disease. *JAMA*. 2014;312:1114–1121.
27. Magnussen H, Bugnas B, van Noord J, Schmidt P, Gerken F, Kesten S. Improvements with tiotropium in COPD patients with concomitant asthma. *Respir Med*. 2008;102:50–56.
28. Welte T, Miravitlles M, Hernandez P, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2009;180:741–750.
29. Hanania NA, Crater GD, Morris AN, Emmett AH, O'Dell DM, Niewoehner DE. Benefits of adding fluticasone propionate/salmeterol to tiotropium in moderate to severe COPD. *Respir Med*. 2012;106:91–101.
30. Lipson DA, Barnhart F, Brealey N, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med*. 2018;378:1671–1680.
31. Hanania NA, Wenzel S, Rosén K, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med*. 2013;187:804–811.
32. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med*. 2015;3:355–366.
33. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018;378:2486–2496.
34. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014;371:1198–1207.
35. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016;388:2115–2127.
36. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388:2128–2141.
37. Hanania NA, Alpan O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med*. 2011;154:573–582.
38. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371:1189–1197.
39. Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med*. 2017;376(25):2448–2458.
40. Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med*. 2018;378:2475–2485.
41. Brightling CE, Bleecker ER, Panettieri Jr RA, et al. Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study. *Lancet Respir Med*. 2014;2:891–901.
42. Dasgupta A, Kjarsgaard M, Capaldi D, et al. A pilot randomised clinical trial of mepolizumab in COPD with eosinophilic bronchitis. *Eur Respir J*. 2017;49:3.
43. Pavord ID, Chanez P, Criner GJ, et al. Mepolizumab for eosinophilic chronic obstructive pulmonary disease. *N Engl J Med*. 2017;377:1613–1629.
44. Yousuf A, Ibrahim W, Greening NJ, Brightling CE. T2 Biologics for chronic obstructive pulmonary disease. *J Allergy Clin Immunol Pract*. 2019;7:1405–1416.
45. Criner GJ, Celli BR, Brightling CE, et al. Benralizumab for the prevention of COPD exacerbations. *N Engl J Med*. 2019. https://doi.org/10.1056/NEJMoa1905248.
46. Busse WW, Bleecker ER, FitzGerald JM, et al. Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. *Lancet Respir Med*. 2019;7:46–59.
47. Corren J, Parnes JR, Wang L, et al. Tezepelumab in adults with uncontrolled asthma. *N Engl J Med*. 2017;377:936–946.
48. Wang C, Liu Q, Chen F, Xu W, Zhang C, Xiao W. IL-25 promotes Th2 immunity responses in asthmatic mice via nuocytes activation. *PLoS One*. 2016;11:e0162393.
49. Mizutani N, Nabe T, Yoshino S. Interleukin-33 and alveolar macrophages contribute to the mechanisms underlying the exacerbation of IgE-mediated airway inflammation and remodelling in mice. *Immunology*. 2013;139:205–218.
50. Tat TS, Cilli A. Omalizumab treatment in asthma-COPD overlap syndrome. *J Asthma*. 2016;53:1048–1050.
51. Yalcin AD, Celik B, Yalcin AN. Omalizumab (anti-IgE) therapy in the asthma-COPD overlap syndrome (ACOS) and its effects on circulating cytokine levels. *Immunopharmacol Immunotoxicol*. 2016;38:253–256.
52. Maltby S, Gibson PG, Powell H, McDonald VM. Omalizumab treatment response in a population with severe allergic asthma and overlapping COPD. *Chest*. 2017;151:78–89.
53. Hanania NA, Chipps BE, Griffin NM, Yoo B, Iqbal A, Casale TB. Omalizumab effectiveness in asthma-COPD overlap: Post hoc analysis of PROSPERO. *J Allergy Clin Immunol*. 2019;143:1629–1633.
54. Casale TB, Luskin AT, Busse W, et al. Omalizumab effectiveness by biomarker status in patients with asthma: evidence from PROSPERO—a prospective real-world study. *J Allergy Clin Immunol Pract*. 2019;7:156–164.
55. Llanos JP, Bell CF, Packnett E, et al. Real-world characteristics and disease burden of patients with asthma prior to treatment initiation with mepolizumab or omalizumab: a retrospective cohort database study. *J Asthma Allergy*. 2019;12:43–58.
56. Mahler DA, Huang S, Tabrizi M, Bell GM. Efficacy and safety of a monoclonal antibody recognizing interleukin-8 in COPD: a pilot study. *Chest*. 2004;126:926–934.
57. Busse WW, Holgate S, Kerwin E, et al. Randomized, double-blind, placebo-controlled study of brodalumab, a human anti-IL-17 receptor monoclonal antibody, in moderate to severe asthma. *Am J Respir Crit Care Med*. 2013;188:1294–1302.
58. Erin EM, Leaker BR, Nicholson GC, et al. The effects of a monoclonal antibody directed against tumor necrosis factor-alpha in asthma. *Am J Respir Crit Care Med*. 2006;174:753–762.
59. Kirsten AM, Förster K, Radeczky E, et al. The safety and tolerability of oral AZD5069, a selective CXCR2 antagonist, in patients with moderate-to-severe COPD. *Pulm Pharmacol Ther*. 2015;31:36–41.
60. O'Byrne PM, Metev H, Puu M, et al. Efficacy and safety of a CXCR2 antagonist, AZD5069, in patients with uncontrolled persistent asthma: a

randomised, double-blind, placebo-controlled trial. *Lancet Respir Med*. 2016; 4:797–806.
61. Evans DJ, Barnes PJ, Spaethe SM, van Alstyne EL, Mitchell MI, O'Connor BJ. Effect of a leukotriene B4 receptor antagonist, LY293111, on allergen induced responses in asthma. *Thorax*. 1996;51:1178–1184.
62. Postma DS, Rabe KF. The asthma-COPD overlap syndrome. *N Engl J Med*. 2015; 373:1241–1249.
63. Bel EH, Ten Brinke A. New anti-eosinophil drugs for asthma and COPD: targeting the trait!. *Chest*. 2017;152:1276–1282.
64. Maselli DJ, Hardin M, Christenson SA, et al. Clinical approach to the therapy of asthma-COPD overlap. *Chest*. 2019;155:168–177.
65. McDonald VM, Fingleton J, Agusti A, et al. Treatable traits: a new paradigm for 21st century management of chronic airway diseases: Treatable Traits Down Under International Workshop report. *Eur Respir J*. 2019;53:5.
66. Shirai T, Hirai K, Gon Y, et al. Combined assessment of serum periostin and YKL-40 may identify asthma-COPD overlap. *J Allergy Clin Immunol Pract*. 2019; 7:134–145.
67. Metz G, Kraft M. Effects of atypical infections with Mycoplasma and Chlamydia on asthma. *Immunol Allergy Clin North Am*. 2010;30:575–585.
68. Maselli DJ, Medina JL, Brooks EG, et al. The immunopathologic effects of Mycoplasma pneumoniae and community-acquired respiratory distress syndrome toxin: a primate model. *Am J Respir Cell Mol Biol*. 2018;58: 253–260.
69. Komiya K, Ohta S, Arima K, et al. Clarithromycin attenuates IL-13-induced periostin production in human lung fibroblasts. *Respir Res*. 2017;18:37.
70. Hara K, Kondo M, Tsuji M, Takeyama K, Tamaoki J. Clarithromycin suppresses IL-13-induced goblet cell metaplasia via the TMEM16A-dependent pathway in guinea pig airway epithelial cells. *Respir Invest*. 2019;57:79–88.
71. Zhao X, Yu FQ, Huang XJ, et al. Azithromycin influences airway remodeling in asthma via the PI3K/Akt/MTOR/HIF-1α/VEGF pathway. *J Biol Regul Homeost Agents*. 2018;32:1079–1088.
72. Kang JY, Jo MR, Kang HH, et al. Long-term azithromycin ameliorates not only airway inflammation but also remodeling in a murine model of chronic asthma. *Pulm Pharmacol Ther*. 2016;36:37–45.
73. Liu Y, Pu Y, Li D, Zhou L, Wan L. Azithromycin ameliorates airway remodeling via inhibiting airway epithelium apoptosis. *Life Sci*. 2017;170:1–8.
74. Pu Y, Liu Y, Liao S, Miao S, Zhou L, Wan L. Azithromycin ameliorates OVA-induced airway remodeling in Balb/c mice via suppression of epithelial-to-mesenchymal transition. *Int Immunopharmacol*. 2018;58:87–93.
75. Baines KJ, Wright TK, Gibson PG, Powell H, Hansbro PM, Simpson JL. Azithromycin treatment modifies airway and blood gene expression networks in neutrophilic COPD. *ERJ Open Res*. 2018;4:4.
76. Hao M, Lin J, Shu J, et al. Clarithromycin might attenuate the airway inflammation of smoke-exposed asthmatic mice via affecting HDAC2. *J Thorac Dis*. 2015;7:1189–1197.
77. Nakamura M, Wada H, Honda K, et al. Clarithromycin ameliorates pulmonary inflammation induced by short term cigarette smoke exposure in mice. *Pulm Pharmacol Ther*. 2015;35:60–66.
78. Kew KM, Undela K, Kotortsi I, Ferrara G. Macrolides for chronic asthma. *Cochrane Database Syst Rev*. 2015;9:CD002997.
79. Reiter J, Demirel N, Mendy A, et al. Macrolides for the long-term management of asthma: a meta-analysis of randomized clinical trials. *Allergy*. 2013;68: 1040–1049.
80. Tong X, Guo T, Liu S, et al. Macrolide antibiotics for treatment of asthma in adults: a meta-analysis of 18 randomized controlled clinical studies. *Pulm Pharmacol Ther*. 2015;31:99–108.
81. Gibson PG, Yang IA, Upham JW, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2017;390:659–668.
82. Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med*. 2011;365:689–698.
83. Uzun S, Djamin RS, Kluytmans JA, et al. Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med*. 2014;2:361–368.
84. Naderi N, Assayag D, Mostafavi-Pour-Manshadi SM, et al. Long-term azithromycin therapy to reduce acute exacerbations in patients with severe chronic obstructive pulmonary disease. *Respir Med*. 2018;138: 129–136.
85. Pomares X, Montón C, Bullich M, et al. Clinical and safety outcomes of long-term azithromycin therapy in severe COPD beyond the first year of treatment. *Chest*. 2018;153:1125–1133.
86. Krishnan JK, Voelker H, Connett JE, et al. Effect of daily azithromycin therapy and adherence on readmission risk in COPD. *Eur Respir J*. 2019;53:3.
87. Vermeersch K, Gabrovska M, Aumann J, et al. Azithromycin during acute COPD exacerbations requiring hospitalization (BACE): a multicentre, randomized, double-blind, placebo-controlled trial. *Am J Respir Crit Care Med*. 2019. https://doi.org/10.1164/rccm.201901-0094OC.
88. Milito C, Pulvirenti F, Cinetto F, et al. Double-blind, placebo-controlled, randomized trial on low-dose azithromycin prophylaxis in patients with primary antibody deficiencies. *J Allergy Clin Immunol*. 2019. https://doi.org/10.1016/j.jaci.2019.01.051.
89. Taylor SL, Leong LEX, Mobegi FM, et al. Long-term azithromycin reduces Haemophilus influenzae and increases antibiotic resistance in severe asthma. *Am J Respir Crit Care Med*. 2019. https://doi.org/10.1164/rccm.201809-1739OC.
90. Albert RK, Schuller JL. Macrolide antibiotics and the risk of cardiac arrhythmias. *Am J Respir Crit Care Med*. 2014;189:1173–1180.
91. Henriksen DP, Davidsen JR, Laursen CB. Nationwide use of theophylline among adults: a 20-year Danish drug utilisation study. *Respir Med*. 2018;140: 57–62.
92. Ram FS, Jardin JR, Atallah A, et al. Efficacy of theophylline in people with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Respir Med*. 2005;99:135–144.
93. Devereux G, Cotton S, Fielding S, et al. Effect of theophylline as adjunct to inhaled corticosteroids on exacerbations in patients with COPD: a randomized clinical trial. *JAMA*. 2018;320:1548–1559.
94. Clinical trial of low-dose theophylline and montelukast in patients with poorly controlled asthma. *Am J Respir Crit Care Med*. 2007;175:235–242.
95. Dahl R, Larsen BB, Venge P. Effect of long-term treatment with inhaled budesonide or theophylline on lung function, airway reactivity and asthma symptoms. *Respir Med*. 2002;96:432–438.
96. Margay SM, Farhat S, Kaur S, Teli HA. To study the efficacy and safety of doxophylline and theophylline in bronchial asthma. *J Clin Diagn Res*. 2015;9: FC05–8.
97. Calzetta L, Hanania NA, Dini FL, et al. Impact of doxofylline compared to theophylline in asthma: a pooled analysis of functional and clinical outcomes from two multicentre, double-blind, randomized studies (DOROTHEO 1 and DOROTHEO 2). *Pulm Pharmacol Ther*. 2018;53:20–26.
98. Martinez FJ, Calverley PM, Goehring UM, Brose M, Fabbri LM, Rabe KF. Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multicentre randomised controlled trial. *Lancet*. 2015;385:857–866.
99. Martinez FJ, Rabe KF, Sethi S, et al. Effect of roflumilast and inhaled corticosteroid/long-acting β2-agonist on chronic obstructive pulmonary disease exacerbations (RE(2)SPOND): a randomized clinical trial. *Am J Respir Crit Care Med*. 2016;194:559–567.
100. Rabe KF, Calverley PMA, Martinez FJ, Fabbri LM. Effect of roflumilast in patients with severe COPD and a history of hospitalisation. *Eur Respir J*. 2017;50:1.
101. Luo J, Yang L, Yang J, et al. Efficacy and safety of phosphodiesterase 4 inhibitors in patients with asthma: a systematic review and meta-analysis. *Respirology*. 2018;23:467–477.
102. Chervinsky P, Meltzer EO, Busse W, et al. Roflumilast for asthma: safety findings from a pooled analysis of ten clinical studies. *Pulm Pharmacol Ther*. 2015;35(suppl 1):28–34.
103. Martinez FJ, Rabe KF, Calverley PMA, et al. Determinants of response to roflumilast in severe chronic obstructive pulmonary disease. pooled analysis of two randomized trials. *Am J Respir Crit Care Med*. 2018;198:1268–1278.
104. Rabe KF, Watz H, Baraldo S, et al. Anti-inflammatory effects of roflumilast in chronic obstructive pulmonary disease (ROBERT): a 16-week, randomised, placebo-controlled trial. *Lancet Respir Med*. 2018;6(11):827–836.
105. Wells JM, Jackson PL, Viera L, et al. A randomized, placebo-controlled trial of roflumilast: effect on proline-glycine-proline and neutrophilic inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2015; 192:934–942.
106. Freitas PD, Ferreira PG, Silva AG, et al. The role of exercise in a weight-loss program on clinical control in obese adults with asthma. a randomized controlled trial. *Am J Respir Crit Care Med*. 2017;195:32–42.
107. Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIANE Investigators. European Network on Aspirin-Induced Asthma. *Eur Respir J*. 2000;16:432–436.
108. Walters JA, Tang JN, Poole P, Wood-Baker R. Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2017;1:CD001390.
109. Mulpuru S, Li L, Ye L, et al. Effectiveness of influenza vaccination on hospitalizations and risk factors for severe outcomes in hospitalized patients with COPD. *Chest*. 2019;155:69–78.
110. Cates CJ, Rowe BH. Vaccines for preventing influenza in people with asthma. *Cochrane Database Syst Rev*. 2013;2:CD000364.
111. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med*. 2013;188:e13–e64.
112. Castro M, Rubin AS, Laviolette M, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. *Am J Respir Crit Care Med*. 2010; 181:116–124.