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Inside this issue: Asthma-COPD Overlap

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Asthma is a risk factor for respiratory exacerbations without increased rate of lung function decline. Five-year follow-up in adult smokers from the COPDGene study.

Lystra P. Hayden, et al.
Chest 2018. 153:368-77
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5815872/

COPDgene, one of the largest studies to investigate the underlying genetic factors of COPD, enrolled 10,199 current and former smokers with and without COPD in phase 1 from 2008 to 2011. Current study analyzed data from the first 4,915 subjects of the phase 1 cohort, returning for five-year follow-up in phase 2 of COPDgene in 2016. At enrollment of phase 1 of COPDgene, 569 subjects had asthma COPD overlap (ACO) as defined as subjects with COPD who self-reported asthma diagnosed by a health professional with age of onset at ≤40 years or during childhood. COPD was defined as post-bronchodilator FEV1/FVC<0.7 with FEV1<80%. A total of 3,110 had COPD alone. 54% of subjects who had childhood pneumonia and 61% of subjects who had childhood asthma had COPD at enrollment, which were significantly more frequent than those subjects who did not have childhood pneumonia or childhood asthma. Analysis was conducted to assess disease progression in three subject groups: childhood pneumonia, childhood asthma, and ACO on the hypothesis that smokers with childhood pneumonia or childhood asthma might show less lung function decline at the time of five-year follow-up. Disease progression was determined by lung function, clinical symptoms including severity and frequency of respiratory exacerbations, and chest CT scan measurements of emphysema and airway disease.

Among the 4,915 current and former smokers, 407 subjects had childhood pneumonia, 323 had childhood asthma, and 242 had ACO. There was some overlapping among the three categories, for example 39 had all three categories and 113 had ACO and childhood asthma. During the follow-up period, history of childhood asthma (n = 323) or ACO (n = 242) was associated with an increased exacerbation frequency and odds of severe exacerbations in the prior year, when compared with those who did not have childhood asthma (n = 4,563) and with COPD alone (n = 1,359). In subjects with COPD alone, history of childhood pneumonia was associated with an increased exacerbation frequency, when compared with those who did not have childhood pneumonia. However, none of these early-life respiratory diseases were not accompanied with increased rate of lung function decline or progression of emphysema and airway

disease on CT imaging. The authors concluded that there would be an alternative pathway to reach COPD in smokers with early-life respiratory diseases.

For the comparisons between ACO and COPD alone, 25% of subjects with ACO had a severe exacerbation in prior year, while 17% of those with COPD alone had it ($p = 0.006$ in multivariate analysis). Annual declines in FEV1 and FVC of subjects with ACO were -30 mL/year and -44 mL/year, respectively, while those in subjects with COPD alone were -44 mL/year and -59 mL/year, respectively (both $p < 0.001$ in univariate analysis). Progression of emphysema and gas trapping was milder for ACO than COPD alone ($p = 0.02$ and $p = 0.01$, respectively, in multivariate analysis). Attenuated risks of lung function decline and progression of emphysema and gas trapping despite increased exacerbation frequency in smokers with ACO in comparison with smokers with COPD alone may suggest the presence of different mechanisms underlying the development of exacerbation in ACO and COPD alone.

Omalizumab treatment response in a population with severe allergic asthma and overlapping COPD

Steven Maltby, et al.
Chest 2017; 151:78-89
https://doi.org/10.1016/j.chest.2016.09.035

Omalizumab is a humanized anti-IgE monoclonal antibody that specifically binds to the Cε3 region of the Fc fragment of IgE, thus inhibiting the binding between free IgE and high-affinity receptors (FcεRI). This prevents the release of various inflammatory mediators, such as histamine, leukotrienes, and prostaglandins from mast cells and is effective in most patients with severe allergic asthma. These effects could be expected in patients with severe allergic asthma and overlapping COPD (ACO). Based on the Australian Xolair registry (AXR), which was established to evaluate the real-world use of omalizumab in Australia, Maltby et al. reported a promising results with omalizumab treatment in subjects with ACO. Patients suffering from severe allergic asthma and physician-diagnosed COPD showed significant improvements in asthma control and health-related quality of life after omalizumab treatment.

Among 177 participants in the AXR who had baseline and 6-month follow-up data, 17 patients were diagnosed as having ACO by physicians. At baseline, there were no significant differences between patients with ACO and those without overlapping COPD, except for age and frequencies of ever-smokers and eczema. Age and frequencies of ever-smokers and eczema

were all greater for patients with ACO than their counterparts (62.3 vs 50.3 years of age, p = 0.002; 66.7% vs 25.3%, p = 0.002; 29.4% vs 10.6%, p = 0.026). Average pack-year of patients with overlapping COPD was 25. Both the five-item Asthma Control Questionnaire (ACQ)-5 and the Asthma Quality of Life Questionnaire (AQLQ) score improved significantly with exceeding the minimal clinically important difference in AQLQ. The extent of improvement in ACQ-5 and AQLQ was similar to that of patients without overlapping COPD. However, lung function did not improve at 6-month follow-up. These findings were consistently observed in population enriched for ACO based on post-bronchodilator FEV1 (%FEV1 < 80%, n = 55) and smoking history (n = 11).

Similar findings were observed in patients with ACO treated with omalizumab in the Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab (PROSPERO) (Hanania NA, et al. J Allergy Clin Immunol 2019.143:1629-33). In PROSPERO, patients with physician diagnosed or self-reported COPD were defined as having ACO A (n = 56), and patients with post-bronchodilator FEV1/FVC<0.7 and smoking history (10 pack-year or more) were defined as having ACO B (n = 50). Average pack-year was 22.5 for ACO A and 27.7 for ACO B. According to the study design, patient groups of ACO A and B were independent and mutually exclusive. Asthma exacerbations were significantly reduced and asthma control was significantly improved in both ACO A and B after omalizumab treatment, similarly to their counterparts (n = 681 and 663). However, the impact of omalizumab treatment on improvement in lung function was limited in ACO. Omalizumab may improve asthma control and quality of life, but not lung function, in severe allergic asthma overlapping COPD in real world.

Asthma and COPD overlap (ACO) is related to a high burden of sleep disturbance and respiratory symptoms: Results from the RHINE and Swedish GA^{2}LEN surveys

Mindus S, et al.
Reference PLOS ONE 2018. 13:e0195055
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0195055

According to two northern European general population surveys, i.e. the Global Allergy and Asthma Network in Europe (GA^{2}LEN)(n = 13,967) and Respiratory Health in Northern Eu-

rope (RHINE)(n = 11,462), subjects with asthma COPD overlap (ACO) had both insomnia and respiratory symptoms more frequently than subjects with only asthma or COPD. Among subjects who participated in either of the two surveys, prevalence of ACO that was defined as having both self-reported asthma and COPD was 1.0%, while prevalence of asthma and COPD was 6.5% and 1.4%, respectively. Sleep-related symptoms, i.e. difficulty in initiating sleep, difficulty in maintaining sleep, early-morning awakening, and excessive daytime sleepiness were 2-3 times more frequent in subjects with ACO, when comparing with those with only asthma or COPD: the frequencies of sleep-related symptoms above mentioned were 37.3%, 53.9%, 39.7%, and 45.2% in ACO, respectively. These increased sleep-related symptoms were accompanied with greater frequencies of respiratory symptoms: wheeze, nocturnal chest tightness, nocturnal breathlessness, nocturnal cough and chronic bronchitis.

Biological exacerbation clusters demonstrate asthma and chronic obstructive pulmonary disease overlap with distinct mediator and microbiome profiles

Ghebre MA, et al.
Reference J Allergy Clin Immunol 2018. 141:2027-36
https://doi.org/10.1016/j.jaci.2018.04.013

Culture-independent techniques have revealed the presence of a microbiome in the lower airways of normal subjects that have been considered sterile for a long time. In this single center study, inflammatory mediators and microbiome patterns in the lower airways at exacerbations were examined in 32 patients with severe asthma and 73 patients with moderate to severe COPD. Asthmatic patients were younger and more obese and had maintenance prednisolone more frequently, fewer pack-year history and better lung function than patients with COPD. Other clinical indices including inhaled corticosteroid doses were not significantly different between the two diseases. Cluster analysis using sputum mediators at exacerbation for all patients with severe asthma and COPD that were reduced by factor analysis provided three distinct biologic clusters; Cluster 1, COPD-predominant, neutrophilic, bacteria associated, pro-inflammatory mediators and proteobacteria predominant; Cluster 2, eosinophilic and type-2 inflammatory mediators in sputum; Cluster 3, viral-associated, type-1 inflammatory mediators such as CXCL10 in sputum, and infrequent proteobacteria. Across the three clusters, differ-

ences in age, body mass index, maintenance prednisolone dose, pack-year history, and lung function between severe asthma and COPD remained significant. In addition, cluster 1 was defined as COPD-predominant, but still 7 severe asthmatics (22% of severe asthmatics) were included in this cluster. Cluster 2, which was characterized by increased sputum and blood eosinophil counts and elevated levels of sputum IL-5, IL-13, CCL13, CCL17 and CCL-26 and serum IL-5 and CCL26, included 10 asthmatics (31%) and 17 patients with COPD (23% of COPD). Cluster 3 included 15 asthmatic (47％) and 29 patients with COPD (40% of COPD).

This study did not intend to delineate biologic mediators and microbiome patterns of a patient group of asthma and COPD overlap, in comparison with patients with asthma or those with COPD. However, this study demonstrated that despite several phenotypical differences between severe asthma and COPD, biological and microbiome patterns at exacerbations were shared between the two diseases across the three distinct clusters. Therefore it is possible to speculate that asthma-COPD overlap may be heterogeneous, and have different biological microbiome patterns at exacerbations as shown in groups of severe asthma and COPD.

Childhood predictors of lung function trajectories and future COPD risks: a prospective cohort study from the first to the sixth decade of life

Bui, et al.
Lancet Respir Med 2018
https://doi.org/10.1016/S2213-2600(18)30100-0

It has been known that early life factors, such as maternal smoking and childhood asthma, affect lung function trajectories, but previous studies provided the trajectories at most into an early adulthood and on single phases of lung function trajectories. The Tasmanian Longitudinal Health Study (TAHS), a population-based cohort study, started in 1968 when 8583 Tasmanian children born in 1961, followed up subjects at ages of 13, 18, 45, 50 and 53 years. From the 8583 participants in an original cohort of TAHS, 2438 subjects who had lung function data at least at ages of 7 years and 53 years were assessed in this study, and were determined their FEV_1 trajectories into the sixth decade. The TAHS identified six lung function trajectories; ①early below average and accelerated decline (4% of participants), ②persistently low (6%), ③early low but accelerated growth with normal decline (8%), ④persistently high (12%),

⑤below average (32%), and ⑥average (39%). Three trajectories (①early below average and accelerated decline, ②persistently low, ⑤below average) had increased risk of COPD, as defined as post-bronchodilator FEV_1 /FVC less than the lower limit of normal, at 53 years compared with the average group ⑥. Subjects with trajectory ① were more likely to have childhood asthma, bronchitis, eczema, allergic rhinitis, pneumonia or pleurisy and a heavy smoking mother. Subjects with trajectory ② were more likely to have childhood asthma, eczema and parental asthma. Trajectory ⑤ was associated with childhood pneumonia or pleurisy. Subjects with asthma alone and asthma-COPD overlap were enriched in two trajectories (①②). Among all cases of COPD (n = 119) at 53 years, the population-attributable fractions for trajectories ①, ②, and ⑤ were 35.4%, 12.6%, and 27.2%, respectively: these three trajectories contributed 75% of COPD at 53 years. Among all cases of ACO (n = 57), crude fractions for trajectories ①, ②, and ⑤ were 43.8%, 24.6%, and 24.6%, respectively, while among all cases of asthma (n = 517), crude fractions for trajectories ①, ②, and ⑤ were 10.8%, 10.3%, and 34.6%, respectively.

Thus childhood asthma, bronchitis, eczema, allergic rhinitis, pneumonia or pleurisy, a heavy smoking mother, or a parental asthma are strong risk factors of ACO in middle-aged adults. Of interest, the same TAHS cohort found that a history of childhood measles infection that was obtained from school medical records was another risk factor of post-bronchodilator airflow obstruction in middle-aged adults (Perret JL, et al. Respirology 2018;23:780-7; Hancox and Zhang. Respirology 2018;23:731-2). The effect of history of childhood measles infection on airflow obstruction was increased by the presence of current asthma and smoking history of ≥ 10 pack-years (three-way interaction, p = 0.0009). Measles virus has long-lasting effects on immune function, which might explain this interaction, but further study is necessary. In addition, when considering that multiple inflammatory hits may be necessary for the development of chronic airflow limitation, unknown components that may accelerate airflow limitation, resulting in ACO in middle-aged adults, should be further determined.

Physiological and morphological differences of airways between COPD and asthma-COPD overlap

Karayama, et al.
Sci Rep 2019; 9: 7818
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6534606/

Asthma COPD overlap (ACO) is a heterogeneous disease that is more difficult to control and is characterized by more frequent exacerbations than asthma or COPD alone. Physiologically, the presence of variable airflow limitation is an important feature of ACO and is often used in a criteria of ACO. Karayama et al. further clarified physiological and morphological features of ACO using respiratory impedance at inspiratory and expiratory phases and 3-D computed tomography (CT) analysis of the chest. In short, patients with ACO (n = 43) had higher respiratory resistance and reactance during tidal breathing, but a smaller gap between the inspiratory and expiratory phases, than patients with COPD (n = 86). In addition, patients with ACO showed a greater airway wall thickness in third to fourth generation bronchi, smaller airway luminal area in fifth to sixth generation bronchi, but less emphysematous changes than patients with COPD.

Advantage of this study is the well-balanced population with ACO and COPD in terms of smoking history and fixed airflow limitation, which was yielded by a propensity score-matched analysis using age, sex, BMI, and pack-year smoking. First, in this study, patients with ACO were recruited from patients with COPD who satisfied the definition of COPD by GOLD. ACO was defined by a history of variable respiratory symptoms (wheeze, shortness of breath, chest tightness, or cough) and the presence of variable expiratory airflow limitation (increase in percentage predicted FEV1 of >12% and FEV1 of 200 mL after a postbronchodilator or 4 weeks of anti-inflammatory treatment). Thus patients with ACO and COPD had similar degree of smoking exposure (39.8 pack-year for ACO and 45.7 for COPD) and percentage predicted FEV1 (69.4% for ACO and 70.3% for COPD). Although the degree of airflow limitation was moderate in both ACO and COPD in this study, the findings are informative to speculate that there is a greater contribution of airway wall thickening and small airway narrowing to airflow limitation in ACO and a greater contribution of emphysematous changes to airflow limitation, particularly during expiratory phase of breathing, in COPD. Shirai, et al. reported similar findings in un-matched patients with COPD and ACO (Forced oscillation technique may identify asthma-COPD overlap. Allergol Int 2019 Epub ahead of print. doi: 10.1016/j.alit.2019.01.002). In that study by Shirai et al., gap of low-frequency reactance area (ALX) in between inspiratory and expiratory phases was significantly different among COPD, ACO and asthma (2.78, 1.88, and 0.19 cmH2O/L/s x Hz for COPD, ACO, and asthma, respectively) ($p < 0.001$). These findings support that greater gap of reactance

in between inspiratory and expiratory phases in COPD than in ACO would be an important physiological difference between ACO and COPD.

Nitrosative stress in patients with asthma-chronic obstructive pulmonary disease overlap

Kyogoku, et al.
J Allergy Clin Immunol 2019 in press
https://doi.org/10.1016/j.jaci.2019.04.023

The authors previously showed the presence of excessive nitrosative stress in patients with COPD and severe asthma, which resulted in airway inflammation, tissue injury, tissue fibrosis, and activation of matrix metalloproteinases. Here they newly examined nitrosative stress in the airways of patients with asthma COPD overlap (ACO), and its correlation with clinical courses afterwards. They also examined potent antioxidants of reactive persulfides and polysulfides, and their synthases; cystathionine β-synthase (CBS) and cystathionine γ–lyase (CSE) in the airways of patients with ACO.

The average age, smoking pack-years, FEV1 percent predicted value and FEV1/FVC of patients with ACO (n = 23) were 71.2 years, 49.1, 64.2% and 54.6%, respectively. For patients with asthma (n = 33), these were 65.7 years, 13.5, 99.1%, and 78.0%, respectively.

Expression of inducible nitric oxide synthase (iNOS) and 3-nitrotyrosine (3-NT), markers of nitrosative stress, were significantly increased in patients with ACO than healthy subjects or asthmatic patients, positively associated each other, and both negatively correlated with FEV1 percent predicted values. Contrary, the expression of reactive persulfides and polysulfides, and their synthases of CBS and CSE were all significantly decreased in patients with ACO than healthy subjects or asthmatic patients, and negatively associated with 3-NT positive cells. As for association with future clinical courses, expression of iNOS and 3-NT was negatively associated with annual changes in FEV1 and positively associated with frequencies of exacerbations. Frequencies of exacerbations were negatively associated with the extent of reactive persulfides and polysulfides expression. Finally, several proinflammatory chemokines and cytokines, such as IL-8, monocyte chemotactic factor (MCP) 1, and TNF-α were increased in the airways of patients with ACO than healthy subjects or asthmatic patients, and these chemokines and cytokines were positively associated with 3-NT positive cells. In the airways of pa-

tients with ACO, nitrosative stress is increased, while antioxidant is decreased. These may lead to poorer clinical course and might explain the pathogenesis of ACO.

ACO: time to move from the description of different phenotypes to the treatable traits

Toledo-Pons N, et al.
PLOS ONE 2019; 14: e0210915
https://doi.org/10.1371/journal.pone.0210915

Asthma-COPD overlap (ACO) is an important disease entity, which had been excluded from studies of asthma or COPD for a long period but recently become a renewed focus of interest. Currently many studies have tried to clarify the pathogenesis, optimal management and medications of ACO. However, the lack of universal definition of asthma-COPD overlap (ACO) precludes us from interpretation and comparisons of such studies. In this study of the MAJORICA cohort, where patients with a diagnosis of asthma and/or COPD were analyzed, they determined ACO with several criteria in a sequential manner, similar to an algorithm proposed by the Spanish Respiratory Society (SEPAR). A total of 603 patients fulfilled all criteria of ≥ 40 years of age, post-bronchodilator FEV1/FVC < 0.7, and smoking exposure > 10 pack-years. Among the 603 patients, firstly patients with physician diagnoses of asthma were identified (smoking asthmatics, n = 83). Secondly patients with a high bronchodilator response (>400 mL and 15% in FEV1) were identified (n = 9), and thirdly those with blood eosinophil count greater than 300 cells/μL were identified (COPD-Eo, n = 73). The remaining patients were classified as COPD cases (no-ACO, n = 438). Of interest, 5 of patients with a high bronchodilator response had blood eosinophil count greater than 300 cells/μL and included in COPD-Eo. Therefore, finally there were two conditions in ACO, i.e. smoking asthmatics and COPD-Eo. Smoking asthmatics were younger, relatively more often women, and they presented more asthma-related comorbidities (allergic rhinitis and gastroesophageal reflux) than patients with COPD-Eo. Consistent with previous CHACOS studies reported by Cosio and colleagues (Cosio, et al. Eur Respir J 2017;49:1602397), there were no differences in lung function, and smoking asthmatics showed greater use of oral and inhaled corticosteroids and lower blood eosinophil counts, smoking asthmatics had more frequent hospitalizations than patients with COPD-Eo. Furthermore, among smoking asthmatics,

COPD-Eo, and no-ACO, frequencies of emergency visits and hospitalization were the lowest in COPD-Eo than in smoking asthmatics or no-ACO.

Several findings of MAJORICA cohort are consistent with those of CHACOS studies reported by Cosio and colleagues (Cosio, et al. Eur Respir J 2017;49:1602397; Perez-de-Llano, et al. Respir Res 2017;18:183), leading to the conclusion that ACO is a heterogeneous disorder and includes two entities with a different inflammatory patterns and clinical characteristics: smoking asthmatics and COPD-Eo. In both MAJORICA and CHACOS, patients with COPD-Eo are older and more likely to be male, and show higher blood eosinophil counts than smoking asthmatics, although tobacco exposure is relatively low in MAJORICA (9 pack-years for COPD-Eo in MAJORICA and 51.8 pack-years for COPD-Eo in CHACOS).

Comparative effectiveness of LABA-ICS versus LAMA as initial treatment in COPD targeted by blood eosinophils: a population-based cohort study

Suissa S, et al.
Lancet Respir Med 2018; 6: 855-62
https://www.clinicalkey.com.au/#!/content/journal/1-s2.0-S2213260018303680

A number of recent studies have shown that blood eosinophil count is a marker of responsiveness to inhaled corticosteroids (ICS) in patients with COPD when added to regular use of bronchodilator treatment. However, there is also a concern of increased risk of pneumonia during ICS treatment. In addition, there is no real-world study data on head-to-head comparison of the effectiveness and safety on the long-acting beta agonist (LABA)-ICS and long-acting muscarinic antagonist (LAMA), which was examined in this study. This cohort study used a primary care database from the UK that contained primary care medical records, and included all patients with a COPD diagnosis who newly started long-acting bronchodilators, either LABA-ICS or LAMA. The primary outcome of this study was the first moderate or severe COPD exacerbation to occur after cohort entry. Moderate and severe COPD exacerbations were defined as that needed a new prescription of prednisolone and that needed hospitalization for COPD, respectively. By a propensity score matching analysis using age, sex, and previous exacerbation for matching, the same number (n = 12,366 for each group) of LABA-ICS initiators and LAMA initiators were analyzed. 43.7% of LABA-ICS cohort had ever-diagnosed asthma and 33.2% of LAMA cohort had it, and the proportion

was not significantly different (p = 0.217). Overall, LABA-ICS cohort showed similar incidence of moderate or severe COPD exacerbation in the first year of LABA-ICS use, when compared with LAMAs cohort (HR 0.95 [95%CI 0.90-1.01]). The risk of moderate or severe COPD exacerbation in the first year of medication use was significantly lower in patients with blood eosinophil greater than 4% for LABA-ICS cohort (HR 0.79 [95%CI 0.70-0.88]). Similar risk reduction of moderate or severe COPD exacerbation for LABA-ICS cohort was observed, when the threshold of blood eosinophil count was set at 300 cells/μL; HR 0.76 [95%CI 0.67-0.85]). Meanwhile, incidence of patients admitted to hospital with pneumonia was increased for LABA-ICS cohort, which was similarly observed across the blood eosinophil levels: overall HR 1.37 (95%CI 1.17-1.60), eosinophil <2% HR 1.30 (1.02-1.66), eosinophil 2-4% HR 1.66 (1.28-2.16), eosinophil>4% HR 1.16 (0.4-1.60), when LAMA cohort was used as reference (1.00).

This cohort study showed that blood eosinophil >300 cells/μL or 4% may identify patients who would benefit from LABA-ICS initiation than LAMA initiation, while for patients with blood eosinophils lower than these threshold, LAMA inhaler is preferred because of the risk of pneumonia associated with ICS use. Lastly, these thresholds of blood eosinophil counts are generally accepted. Nonetheless, we should take into account variability of blood eosinophil counts because a number of factors, such as consuming a light meal or exercise, affect within-subject variability and may reduce blood eosinophil counts (Gibson PG. Respirology 2018;23:12-3).

Asthma-COPD overlap: identification and optimal treatment

Cosio BG, et al.
Ther Adv Respir Dis 2018;12:1-11
https://doi.org/10.1177/1753466618805662

Cosio, et al. demonstrated that asthma-COPD overlap (ACO) is an umbrella term that covers at least two different endo-phenotypes; smoking asthmatics and COPD with high eosinophil group (COPD-Eo). There is no universal definition of asthma-COPD overlap (ACO), but whichever diagnostic criteria is used, these two different ACO subtypes may be identified. In both subtypes of ACO, introduction of ICS or other small molecules would be recommended as shown in this review and another one (Maselli, et al. Chest 2019;155:168-77).

For ICS use, smoking asthmatics should use ICS as far as the patients are diagnosed as having asthma. Addition of ICS to bronchodilators is recommended in patients with COPD-Eo, too, but not in patients with lower blood eosinophil counts (Suissa S, et al. Lancet Respir Med 2018; 6: 855-62). For uncontrolled ACO, azithromycin might be another therapeutic option, because azithromycin significantly reduce exacerbations in patients with uncontrolled asthma, irrespective of blood eosinophil counts. Physicians should be careful for adverse events, such as hearing impairment and abnormal QTc interval. There is also a concern of the development of azithromycin-resistant bacteria, if it is used for a long period. Roflumilast, an oral phosphodiesterase-4 inhibitor, is a promising treatment for uncontrolled ACO, because in an analysis of phase II and III studies in patients with asthma, roflumilast, particularly in dose of 500 μg, generally showed improvement in FEV1.

Different from ICS and other small molecules, smoking asthmatics and COPD-Eo might be separately discussed in the treatment of monoclonal antibodies. Several studies show omalizumab improves asthma control and reduces asthma exacerbations in severe allergic asthma with COPD. Meanwhile, phase III studies of anti-IL-5 receptor alpha antibody (benralizumab) for COPD did not reduce annualized rate of COPD exacerbations, even in patients with blood eosinophil counts ≥ 220/μL (Criner GJ, et al. N Engl J Med 2019, Epub ahead of print). In a post-hoc analysis of phase III studies of anti-IL-5 antibody (mepolizumab), when analysis was confined to patients with blood eosinophil counts ≥ 300/μL (COPD-Eo), annualized rate of COPD exacerbations was lower for mepolizumab than placebo (Pavord, et al. N Engl J Med 2017; 377:1613-29). However, the rate was 23% (rate ratio, 0.77; 95% CI, 0.63 to 0.94), which was numerically smaller than that in severe eosinophilic asthma (47%). Against our expectations, the role of anti-IL-5/IL-5 receptor in prevention of exacerbations might be limited in COPD-Eo, but further analysis including other monoclonal antibodies is necessary.

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