Editorial

Severe asthma and asthma-COPD overlap: a double agent or identical twins?

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Background

Since the joint project of asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome first released by the Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD), numerous debates have been triggered. However, the term asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS) remained controversial. Furthermore, ACOS is replaced by asthma-COPD overlap (ACO) and the concept of a syndrome is no longer advised in GINA 2017. In 1961, "Dutch hypothesis" promulgated that the various forms of airway obstruction, including asthma, chronic bronchitis, and emphysema, should be considered as different expressions of one disease entity (1). Conversely, the opposing "British hypothesis" cited asthma and COPD as distinct clinical entities, with different inflammatory cells and mediators, in return, different responses to therapy (2). ACOS/ACO is characterized with persistent airflow limitation and airway inflammation, with the symptoms of frequent and intense cough, wheeze, short of breath and dyspnea, leading to elevated morbidity, mortality and tremendous medical burden worldwide (3-5). Notably, these clinical manifestations to certain degree resemble the criteria of severe asthma which is defined by the requirement of high-dose inhaled corticosteroids (ICS) and a second controller (or systemic corticosteroids) to prevent asthma from becoming uncontrolled, or the disease remains uncontrolled despite therapy in European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines (6). Hence, we aim to address the relationship between ACOS/ACO and severe asthma in terms of current available evidence.

Clinical features of ACOS

Asthma, as an atopic disease, usually presents early onset with the typical Th2 lymphocytes (type 2 helper T cell) derived airway and systematic inflammation and good response to ICS (7). In contrast, COPD characterized by fixed airflow limitation, prefers to be a late-onset disease caused by enhanced Th1 inflammatory responding to inhaled noxious particles or gases (8). Sharing the mixed features of both, ACOS stands at the intersection of asthma and COPD, which results in poor cognition and inappropriate management in clinical practice.

A growing body of studies investigated the features of ACOS. Meta analyses reported ACOS subjects were younger, had higher BMI and healthcare utilization, lower health-related quality of life (9,10). ACOS showed more frequent and severe respiratory exacerbations, but less smoking packs compared to COPD (11-13). Chest computed tomography (CT) scan demonstrated that ACOS subjects illustrated greater bronchial wall thickness than COPD, which was positive related with the degree of airway obstruction (12,14). Besides, a good portion of ACOS patients were observed by a prior diagnosis of asthma and other atopic diseases (11,15,16). Similarly, the Investigation of Obstructive Lung Disease (PLATINO) (17) study evaluated the prevalence of asthma, COPD and ACOS. Likewise, subjects with ACOS showed more respiratory symptoms, worse lung function, greater medication usage, and higher rate of hospitalization and exacerbations. Also, 17.2% of subjects with COPD had self-reported previous diagnosis of asthma. In general, though the specific values varied due to inclusion criteria, ACOS subjects were observed to be associated with increased disease severity

(15,18). Additionally, airway hyperreactivity (AHR) is known as a common feature of asthma. Interestingly, approximate 1/2 to 2/3 of patients with COPD demonstrated AHR as well (19,20). COPD with AHR linked to an increased risk of respiratory mortality and an accelerated decline of forced expiratory volume in 1 second (FEV_1) (19,21), particularly in patients with late asthma onset (22), while some disparities existed (23,24). Collectively, persistent airflow limitation with increased AHR, the greater airway remodeling, worse clinical manifestations, poorer therapy response, in conjunction with prior asthma diagnosis, is the sole critical markers for ACO.

ACOS: a phenotype of severe asthma?

Among all asthmatic patients in United States, 5–10% had severe form which contributes to nearly 50% of the healthcare costs of asthma (25,26). Unlike milder disease, severe asthma is poorly controlled by the standard care. The ERS/ATS consensus proposed that asthma, which requires treatment with guideline suggested medications for GINA steps 4–5 for the previous year or systemic corticosteroids for more than half of previous year to prevent it from being uncontrolled or which remains uncontrolled despite this therapy, is defined as severe asthma (6). The guidelines further clarified the conditions attributed to uncontrolled asthma, including poor symptom control, frequent severe exacerbation, serious exacerbation, and airflow limitation. Of note, the definition of severe asthmatic patients with fixed airflow limitation in the ERS/ATS guidelines is overlapped with ACOS. As discussed above, ACOS subjects defined by guidelines and studies have comparable characteristics of severe asthma: earlier onset with worse respiratory symptoms, more exacerbation, lower smoking packs, higher rate of AHR, thicker airway wall as well as a higher overall respiratory morbidity (5,27-29). Hence, we recently raised the concern that more than half of the participants recruited in a dupilumab [anti-interleukin-4 (IL-4) receptor α monoclonal antibody] clinical trial for severe asthma expressed persistent airflow limitation, who also met the diagnostic criteria of ACOS (30,31).

Ghebre and colleagues (32) enrolled 86 severe asthma subjects with the average post-FEV_1 predicted of 79.8%, sputum neutrophil count of 63.2% and sputum eosinophil count of 2.1%. After cluster analysis, 28/86 were filtered into ACOS group, exhibiting the average post-FEV_1 predicted of 74.7%, sputum neutrophil count of 70.1% and sputum eosinophil count of 0.7%. These findings indicated that ACOS is partly overlapped with severe asthma, especially the subgroup characterized with persistent airflow limitation and neutrophilic airway inflammation. Another cohort study enrolled 18,356 young European adults and a 9-year follow-up was carried out (33). They found that ACOS subjects shared the identical risk factors, clinical characteristics, including the annual decline of lung function with asthmatic subjects. However, compared to asthma, ACOS subjects had more respiratory symptoms, a higher rate of medicine usage, hospitalization and exacerbations. In addition, a cross-sectional observational study focusing on moderate-to-severe asthmatics provided a clue that the male dominated, profound smoking group with lower lung function was a unique sub-phenotype of asthma, which is consistent with ACOS (34). However, the controversial remains. Smolonska *et al*. found no common genetic component or different environmental factors in COPD and asthma (35). GINA 2017 suggested ACO didn't refer to an independent disease. Nevertheless, Barnes and colleagues compared the similarities and differences between COPD, asthma and severe asthma. Interestingly, COPD showed similar inflammation profile to severe asthma, including neutrophils, CD8(+) lymphocytes, and some key mediators such as IL-8 and nitric oxide. Both COPD and severe asthma response poorly to steroids (2). These datasets suggest ACOS and severe asthma express high clinical similarities, and further attracted our curiosity that whether ACOS represents a special phenotype of severe asthma?

Therapeutic options for ACOS

Presumably ACOS is a phenotype of severe asthma; we ought to explore the efficacy or effectiveness of severe asthma specific therapy on ACOS. ICS based therapy combined with bronchodilators are generally recommended for both ACOS and severe asthma in the guidelines listed on *Table 1*. However, little benefit was identified for ICS/long-acting β2 agonist (LABA) combination therapy on ACOS patients with severe airflow limitation (36,37). To acquire better therapeutic effects, some attempts have been achieved in the latest explosions, reflecting the rapidly escalating interest in this topic (38,39).

Biologics

Compared to COPD subjects and health control, Th2 inflammatory response was enhanced in ACOS subjects with high levels of IL-4 and immunoglobulin E (IgE) (40).

Table 1 Comparison between ACOS and severe asthma

Variables	ACOS	Severe asthma
Definition	GINA-GOLD guidelines ACOS is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACOS is identified in clinical practice by the features that it shares with both asthma and COPD	Asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy
Diagnostic criteria	GINA-GOLD guidelines A similar number of features of both asthma and COPD, consider the diagnosis of ACOS (a stepwise approach to diagnosis is advised for diagnosis of ACOS) Spanish ACOS guidelines (2 major criteria, or 1 major and 2 minor criteria) Major criteria • Very positive bronchodilator test (increase in FEV_1 ≥15% and ≥400 mL) • Eosinophilia in sputum • Personal history of asthma Minor criteria • High levels of total IgE • Personal history of atopy • Positive bronchodilator test on at least two occasions (increase of FEV_1 >12% and >200 mL) Finish COPD guidelines (2 main criteria, or 1 main and 2 additional criteria) Main criteria • Significant bronchodilatory response (FEV_1 >15% and >400 mL) • Sputum eosinophilia or FeNO >50 ppb • Previous asthma symptoms (starting age at <40 years) Additional criteria • Elevated total IgE • Atopy • Repeated significant bronchodilatory response (FEV_1 >12% and >200 mL) • PEF-follow-up typical to asthma	At least one of the following (I) Poor symptom control: ACQ consistently >1.5, ACT ≤19 (II) Frequent severe exacerbations: 2 or more bursts of systemic CSs (>3 days each) in the previous year (III) Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year (IV) Airflow limitation: after appropriate bronchodilator withhold FEV_1 <80% predicted (in the face of reduced FEV_1/FVC defined as less than the lower limit of normal)

Table 1 *(continued)*

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Variables	ACOS	Severe asthma
	Czech COPD guidelines (2 major criteria or 1 major plus 2 minor criteria)	
	Major criteria	
	• Strong BDT positivity (FEV_1 >15% and >400 mL)	
	• BCT positivity	
	• FeNO ≥45–50 ppb and/or ↑Eos (sputum) ≥3%	
	• History of asthma	
	Minor criteria	
	• Mild BDT positivity (FEV_1 >12% and >200 mL)	
	• Total IgE↑	
	• History of atopy—and definite COPD diagnosis	
Therapy	GINA-GOLD guidelines	Using established asthma medications
	ICS in a low or moderate dose (depending on level of symptoms); add-on treatment with LABA and/or LAMA. If there are features of asthma, avoid LABA monotherapy	• ICS or OCS
	Finish COPD guidelines	• SABA or LABA
	Generally, medication includes at least the following	• Slow release theophylline
	ICS + LABA or ICS + LABA + LAMA	• LTRA
	Spanish ACOS guidelines	• LAMA
	LABA + ICS, LAMA + LABA + ICS	Specific therapeutic approaches
	Czech COPD guidelines	• Monoclonal anti-IgE/IL-5/IL-4/IL-13
	ICS + LABA, ICS + LABA + LAMA, antileukotrienes	• Methotrexate
		• Macrolide antibiotics
		• Antifungal agents (for ABPA)
		• Bronchial thermoplasty

ACOS, asthma-chronic obstructive pulmonary disease overlap; COPD, chronic obstructive pulmonary disease; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LABA, long-acting β2 agonist; OCS, oral corticosteroid; PEF, peak expiratory flow; BDT, bronchial dilation test; BCT, bronchial challenge test; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β2 agonist; ACQ, asthma control questionnaire; ABPA, allergic bronchopulmonary aspergillosis.

Therefore, it is rather interesting to explore the role of cytokine-targeted biologics on ACOS therapy. Treatment with dupilumab, a human anti-IL-4 receptor α monoclonal antibody, resulted in elevated FEV_1, improved symptom control and reduced annual rates of exacerbation in patients with severe asthma (31). We raised the concerns that certain portion of participants eligible for this severe asthma study might be ACOS patients (30). In authors' reply, a *post hoc* analysis about these ACOS subjects was performed: 398 of 755 enriched patients had airflow limitation, and of whom, 92 subjects had significant smoking history (41). Treatment with dupilumab explicitly resulted in improvement of FEV_1 and severe exacerbations in airflow limitation group and furthermore, the subgroup combining with smoking history in line exhibited identical observations. Hence, they concluded dupilumab might function in ACOS patients, including those with smoking history (41). Up to now, monoclonal anti-IgE antibody (omalizumab) and anti-IL-5 monoclonal antibodies (mepolizumab and reslizumab) have been approved by the US Food and Drug Administration (FDA) for treating severe asthma. Similar to dupilumab, a portion of participants enrolled into the clinical trials of these two reagents also represented persistent airflow limitations, who might be ACOS patients (42-44). These patients are probable to benefit from this treatment. Of note, newly released data unraveled that omalizumab dramatically improved symptom control and quality of life in patients with ACOS (45). In concert, some recent observational studies from independent groups reported that ACOS patients experienced lower rates of exacerbation and hospitalization, and fewer symptoms after omalizumab treatment (46-48), although some drawbacks of the study design existed (49). Collectively, biologics could be served as a potential therapeutic approach for ACOS patients, especially, the ones stemming from COPD who have predominantly eosinophilic inflammation and the ones stemming from asthma who are current/former smokers (39). However, this conclusion is warranted to be validated by large-scale, double-blind, randomized clinical trials.

Bronchial thermoplasty

Bronchial thermoplasty (BT) has been approved by the US FDA for the treatment of severe persistent asthma in patients over 18 years (50). BT reduced exacerbations, dose of steroids, emergency department visits, hospitalizations and improved the symptoms of severe asthma (51). The logic of BT is to ablate the excessive airway smooth muscle (ASM) (52).

As the therapeutic target, airway over-thickness was also found in ACOS subjects (12). Possessed the same premise as severe asthma, ACOS might benefit from BT as well. For this, selection of appropriate patients is the most crucial step. In our opinion, suitable group should be limited to ACOS patients who met the criteria of severe asthma, no severe emphysema, age of 18–65 years and pre-bronchodilator $FEV_1 \geq 60\%$ [consulted the inclusion criteria of AIR (53) and AIR2 (54) study]. Moreover, precise estimation of ASM thickness via high resolution CT (HRCT) or optical coherence tomography (OCT) plays a crucial role in the preoperative assessment. It will supply important information showing whether ASM over-thickness is present and which lobe exhibits predominant airway remodeling. The universal excessive ASM might be absent in ACOS patients and the thorough BT treatment (covering upper, lower and lingular lobes) might not be necessary for ACOS subjects.

Macrolides and antifungal agents

Macrolide antibiotics have long been recognized to have anti-inflammatory role on top of their broad-spectrum antibacterial functions (55). It has been applied in both asthma and COPD subjects, showing some beneficial effects (56,57), especially in those with local neutrophilic inflammation (58). Notably, increased airway neutrophils counts were also found in ACOS (32). It is worth to perform a therapeutic trial of macrolide antibiotics in patients with ACOS. On the other hand, higher rate of fungal sensitization was identified in ACOS compared to COPD (59). It could be the underlying cause leading to worse clinical symptoms and unsatisfying therapeutic response in ACOS. Thus far, antifungal agents could be considered as an underlying treatment option for ACOS patients who are specifically allergic to *Aspergillus*.

Conclusions

At present, we could barely differentiate ACO/ACOS from severe asthma by phenotype-based definitions. Accordingly, we made a cautious speculation that ACOS is a phenotype of severe asthma based on available data. However, we adopt a taxonomic view mainly based on clinical observations, but the underlying conceptual framework

is missing. Clinical trials with large cohort from different backgrounds and races are urgently needed to systematically assess the clinical, morphological, physiological, cellular and molecular characteristics between severe asthma and ACOS both stemming from asthma and COPD. Alternatively, the recent emerging concept of disease network module in the interactome (60) could be used to elucidate the relations of severe asthma and ACOS.

Besides, we opined that the targeted approaches for severe asthma may also be functional in ACOS. Importantly, to select appropriate therapy requires precise identification of phenotypes that are predictive of response to specific treatment. So far, expect dupilumab, the direct and compelling evidence is still lacking. We thus first have to make effort on the raw data from previous biologics clinical studies on severe asthma to identify whether some enrolled patients also met ACOS and to confirm the therapeutic effects on these patients. Next, we need to design the specific prospective study to answer the questions. BT is a novel therapy for severe asthma targeting excessive ASM. To test the role of BT in ACOS, we ought to figure out clearly the degree of excessive ASM in advance. HRCT and OCT if available should be employed to estimate the thickness of ASM.

In all, the aim of our idea is not to label but to break the constraint from the traditional frame of chronic airway diseases. Given this, identifying the appropriate patient cohort by multidimensional assessment for each therapeutic approach may share a satisfactory promising treatment of ACOS/ACO. We evaluated accessible evidences and prudently deduced this viewpoint, yet, there is still leeway in debating cognition of ACOS. Our hypothesis is warranted to be validated and further clinical trials are imperative to develop more evidence for the safe and effective disease management.

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Footnote

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