**Asthma features in severe COPD: identifying treatable traits**

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**Aim**

Biological therapies developed for severe asthma may have a role in COPD patients with asthma features.

**Method**

We carried out a prospective, consecutive, cross-sectional analysis of 80 patients with severe COPD GOLD IV/D.

**Results**

We studied 80 patients (48.8% female), aged 57.6±5.1 years, ex-smokers with 35.7±21.2 pack years, BMI 22.3±3.5kg/m2, FEV1 of 0.61±0.2L (21.1±5.6% pred), pO2 52.4±8.4mmHg, and BODE 6.9±1.7. 68% had >2 moderate or severe exacerbations annually. 16.1% (5/31) patients showed FEV1 reversibility of >12% and >200ml despite maximal therapy, 33% (15/45) had FENO ≥22.5ppb, 33% (24/73) had serum IgE ≥100 I.E./ml and there was positive allergen sensitization in 51.5% (35/68). Blood eosinophilia of ≥150 cells/μl was seen in 47% (35/74). Induced sputum showed eosinophilia of ≥2% in 56% (14/24) with respiratory pathogens in 63.8% (30/47). We identified 12 (15%) patients with asthma-COPD overlap. Of these, 10 (83.3%) had frequent exacerbations and these patients had significantly more severe exacerbations requiring NIV or ICU than those without asthma features (p < 0.005).

**Conclusion**

We detected asthma features in a substantial subset of stable patients with severe COPD. Asthma features were associated with more severe exacerbation despite optimal COPD therapy, representing potential candidates for targeted therapy with anti- IgE or anti-IL5.

**Introduction**

According to current GOLD guidelines, chronic obstructive pulmonary disease (COPD) is defined as a preventable and treatable disease characterised by usually progressive airway obstruction, which is not fully reversible [1]. However, COPD is a heterogeneous disease with varying phenotypes leading to differing natural courses and significant morbidity and mortality worldwide.

Recently, there has been increased focus on COPD patients displaying eosinophilic inflammation and asthma features. These patients have a higher risk of exacerbation and hospitalization [2-4] and are more likely to benefit from inhaled corticosteroids than patients with COPD alone [4]. Whilst steroid responsiveness seems to be clear [5,6,7], the prognostic relevance less so [8,9]. Analysis of the ECLIPSE study data for example suggested that subjects with blood eosinophilia persistently ≥2% have less severe COPD [9].

Asthma and COPD overlap (ACO) is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD [10]. Some COPD patients may show eosinophilic airway inflammation without asthma features [6], whilst others may show asthma features without fulfilling the criteria for ACO.

Unsurprisingly, there are no clinical tests that single-handedly help to identify patients with ACO. More than 60% of COPD patients may demonstrate airway hyper-responsiveness and/or significant bronchodilator reversibility, without having an overlap with asthma [11]. Fractional exhaled nitric oxide (FeNO) may be higher in COPD patients with a previous diagnosis of asthma than those with COPD alone [12], albeit with a modest sensitivity and specificity to differentiate ACO from COPD: a cut-off value of > 22.5 ppb has shown a 70% sensitivity and a 75% specificity [13]. And whilst COPD is typically associated with neutrophilic airway inflammation [14], it is thought that up to 40% of patients with COPD have an eosinophilic phenotype [15], defined as a peripheral-blood differential eosinophil count of 2% or more, which equates to approximately 150 to 200 eosinophils per cubic millimeter [16]. High levels of sputum eosinophilia has been associated with more severe COPD [17]. It is accepted that there is a moderate correlation between blood eosinophil count and sputum eosinophil count [14,18] so that the former – through convenience and availability - is more commonly used as a biomarker.

There are several ways of defining ACO [19,20]; one recently published expert consensus definition of ACO [21] includes six criteria, 3 of which are major (persistent airflow limitation with FEV1/FVC < 0.7, at least 10 pack years of tobacco smoking and previous asthma or reversibility >400 mL FEV1) and 3 minor (history of atopy or allergic rhinitis, at least 2 positive bronchodilator tests and ≥300 blood eosinophils per μL) [22] with diagnosis of ACO when all 3 major criteria and 1 minor criteria are present.

Targeting specific inflammatory pathyways is the rationale behind the use of biological therapy in COPD [23]. To date, targeting eosinophilic airway inflammation has shown the most promising results for the use of biologicals in the therapy of COPD. Interleukin 5 (IL-5) – primarily produced by T-helper-2 (Th2) cells and type-2 innate lymphoid cells – has shown ft h integral in the production, maturation and survival of eosinophils [15]. Monoclonal antibodies against IL-5 have a selective inhibitory effect on blood eosinophilia. The meta-analysis ft he METREX and METEO phase III studies for Mepolizumab, the monoclonal antibody against IL-5, in COPD demonstrated a significant reduction in exacerbation rate[16].

The allergic pathway offers another potential target with previous data suggesting that the addition of an anti-Immunoglobulin E (IgE) therapy is effective in reducing exacerbations in those with severe allergic asthma and COPD overlap [24]. Omalizumab acts by binding to serum IgE, reducing mast cell, basophil, dendritic cell, and B-cell responses. Exhaled nitric oxide (FeNO) is considered to be the most important biomarker when targeting IgE[23].

COPD patients with asthma features have largely been excluded from major COPD trials [25], so that research in this field is important. The objective of this study was to examine patients with severe group D COPD in a real-life clinical setting – a group with high mortality following exacerbations and most in need of therapy alternatives - for eosinophilia and asthma features in order to correctly identify a subset of patients who may benefit dramatically from new biological therapies in the future.

**Study design**

The study was approved by the ethics committee of the Ludwig-Maximillians University of Munich (Number: 382-10) All patients provided written consent prior to participation in the trial. The study was conducted within the department of internal medicine V at the university hospital Munich. Consecutive patients aged over 18 with an FEV1/FVC quotient of < 70% and an FEV1 of ≤ 30% or a clinical diagnosis of COPD Stage 4 on optimal therapy were approached for entry to the study during a stable phase of disease (at least 4 weeks after last exacerbation). Patients were required to be non-smokers for at least 6 months. Exclusion criteria included the presence of a medical or psychiatric illness that impeded informed consent or a significant concomitant lung disease such as lung fibrosis, severe bronchiectasis or lung cancer.

Lung function entailed whole body plethysmography (pre- and post-bronchodilator with 200μg Salbutamol via metered-dose inhaler; regular bronchodilator therapy not paused), diffusion capacity of the lung for carbon monoxide (DLCO), resting capillary blood gas analysis without supplemented oxygen, skin prick test with standard allergens, fractional exhaled nitric oxide (FeNO) and the 6-minute walking distance (6MWD). Blood tests including differential blood count, total serum IgE and serum-specific IgE (Immunocap) were measured. IgA, IgM, IgG and IgG subclasses were measured to exclude secondary causes of recurrent respiratory infections and exacerbations. As part of the pre-transplantation work-up, a high-resolution computed tomography (HRCT) chest was carried out and evaluated for the presence of bronchiectasis and right-heart catheterization (RHC) was used to assess for the presence of pulmonary hypertension (PH). Routine sputum samples were analyzed for microbiology and in addition, all patients were approached for - and a subset of patients consented for - induced sputum allowing analysis for cell differentiation as well as microbiology. A detailed history was taken, particularly regarding atopy or childhood asthma and allergy as well as the number of exacerbations of COPD in the past 12 months. An exacerbation was defined as a period of increased shortness of breath with the intake of oral antibiotics or steroids or hospital admission (moderate or severe exacerbation). Frequent exacerbation was denoted as 2 or more in the previous 12 months or ≥ 1 leading to hospitalization. The BODE index was determined for all patients.

**Statistical analysis.**

Descriptive statistics were used to summarize the baseline characteristics of the study patients. Fisher’s exact tests or chi-squared tests and Mann-Whitney U-tests were applied to test for statistically significant differences within the cohort. All comparisons were two-tailed and p-values <0.05 were considered significant. A cluster analysis was carried out using K-means clustering and complete-linkage clustering. The statistical tool R was employed.

**Results**

Study cohort

80 patients (39 female) with severe COPD were recruited during the period of September 2015 to April 2017. The majority of patients presented for evaluation for lung transplantation. There were no active smokers and all were in a stable phase of the disease. Baseline characteristics are presented in table 1.

**Table 1:** Baseline characteristics

|  |  |
| --- | --- |
| **Total patients** | **80** |
| Age (years) | 57.6 ± 5.1 (range 46-69) |
| Male (n)Female (n) | 41 (51.3%)39 (48.8%) |
| BMI (kg/m2) | 22.3 ± 3.5 (range 16.7-29) |
| BODE INDEX | 6.9 ± 1.6 (range 3-10) |
| Smoking pack years * Ex-smoker
* Never smoker
 | 35.7 ± 21.2 (range 0-120)77/80 (96.25%)3/80 (3.75%) |
| Long term oxygen therapy (LTOT) | 76/80 (95%) |
| Non-invasive ventilation (NIV) | 38/80 (47.5%) |
| Exacerbation/year (moderate or severe) <2 (infrequent) ≥2 (frequent)Exacerbation with hospitalization (severe) With NIV With ICU | 26/80 (32.5%)54/80 (67.5%)33/80 (41.3%)21/33 (63.6%)16/33 (48.5%) |
| Co-morbidity* Coronary heart disease
* Diabetes
* Cerebrovasular disease
* Arterial hypertension
* Hypercholesterolemia

(Cholesterol normal=120-240mg/dl) * Overweight (BMI 25-30 kg/m2)
* Adiposity Stage 1-3 (BMI > 30 kg/m2)
 | 30 (37.5%)2 (2.5%)2 (2.5%)28 (35%)29 (36.25%)232 (range 149-365)20 (25%)0 |
| Inhaled Therapy* LABA
* LAMA
* ICS
* Triple therapy
 |  80 (100%)77 (96.3%)56 (70%)54 (67.5%) |
| Systemic therapy* Prednisolone
* Roflumilast
* Azithromycin
* Theophylline
 | 31 (38.8%)28 (35%)11 (13.8%)8 (10%) |
| Pulmonary rehabilitation in the previous 3 years | 52 (65%) |

Figures denote mean ± SD values

BMI = body-mass index; LABA = long acting β-2 agonist, LAMA= long acting muscarinic antagonist, ICS = inhaled corticosteroid

Table 2 summarizes the lung function parameters of this group of patients with severe airway obstruction with a mean FEV1 of 21.1 ± 5.6% predicted (absolute FEV1 = 0.61 ± 0.2L), increased residual volume (RV) and total lung capacity (TLC) as well as a severely reduced DLCO (DLCO could not be measured in many of the severely ill patients). There was severe hypoxemia with 95% of patients on long-term oxygen therapy (LTOT) and 47.5% requiring home non-invasive ventilation (NIV) therapy. The mean 6MWD was severely reduced at 246.9 ± 113.6m.

**Table 2:** Overview of lung function

|  |  |
| --- | --- |
| FEV1 (L) | 0.61 ±0.2 (n=80) |
| FEV1 (% predicted) | 21.1 ± 5.6 (n=80) |
| VC (% predicted) | 49.4 ± 16.4 (n=80) |
| RV (% predicted) | 304.5 ± 73.2 (n=76) |
| TLC (%predicted) | 139.4 ± 23.4 (n=76) |
| DLCO (% predicted) | 25.7 ± 12.3 (n=26) |
| Resting capillary pO2 (mmHg) without supplementary oxygen | 52.4 ± 8.4 (n=63) |
| Resting capillary pCO2 (mmHg) without supplementary oxygen | 43.8 ± 6.5 (n=63) |

Figures denote the mean± SD

FEV1 = forced expiratory volume in 1 second, VC = vital capacity, RV = residual volume, TLC = total lung capacity, DLCO = diffusion capacity of the lung for carbon monoxide pO2 = partial pressure of oxygen, pCO2 = partial pressure of carbon dioxide

Asthma features

A summary of asthma features in this cohort of patients with severe COPD is presented in table 3.

**Table 3:** Asthma features in patients with severe COPD

|  |  |  |  |
| --- | --- | --- | --- |
| History of atopy* History of asthma
* Rhino-conjunctivitis
* Atopic dermatitis
 | 29/80 (36.3%)15113 |  |  |
| Allergen specific IgE positive (skin prick or serum)* Skin prick test positive
* Serum test positive
 | 35/68 (51.5%)18/54 (33.3%)26/57 (45.6%) | \*5/18 \*7/26  | \*\*16/36\*\*12/31 |
| Total serum IgE (IU/ml)* IgE ≥ 30 (IU/ml)
* IgE ≥ 100 (IU/ml)
 | Median 41.5 (<4-966)44/73 (60.3%)24/73 (32.9%) | \*16/44\*9/24  | \*\*14/29\*\*21/49 |
| Blood eosinophilia* absolute (Eos/µL)
* percent
* ≥ 2%
* ≥ 3%
* ≥ 150 Eos/µL
* ≥ 300 Eos/µL

Sputum eosinophilia * ≥ 2%
* ≥ 3%

Blood or sputum eosinophilia ≥ 2% | 188.7 ± 159.6 (0-830) 2.5 ± 2.21 44/75 (58.7%)28/75 (37.3%) 35/74 (47.2%) 14/74 (13.5%) 14/24 (58.3%)10/24 (41.7%)48/77 (62.3%)  | \*13/44\*7/28 \*9/35 \*3/14 \*5/14 \*2/10 \*14/29  | \*\*15/31\*\*21/47\*\*19/39\*\*5/11\*\*8/14 |
| Bronchodilator response (BDR)* 12% increase in FEV1
* > 12% + >200ml in FEV1
 | 14/31 (45.2%)5/31 (16.1%)  | \*5/14\*2/5  | \*\*7/17\*\*10/26 |
| Exhaled nitric oxide (ppb)* ≥ 22.5
* > 50 ppb
 | 20.2 ± 15.615/45 (33.3%) 2/45 (4.4%) |  |  |

Figures denote the mean ± SD

\*number of patients positive for criteria despite taking systemic corticosteroids

\*\* number of patients negative for the criteria but taking corticosteroids

14 patients displayed a bronchodilator response (BDR) of > 12% following bronchodilation, although only 5 of these displayed an absolute increase in FEV1 of > 200ml. All 14 patients had an initial FEV1 of <1L absolute. Only 1 patient had an increase of > 400ml.

25 of the overall 35 patients with blood eosinophilia of ≥ 150 cells/µl reported frequent exacerbations (potential criteria for treatment with anti-IL5). 13.5% (n = 14) of patients showed blood eosinophilia levels of ≥ 300 cells/μl. 5 patients had blood eosinophilia of ≥ 400 cells/µl, 4 of these with frequent exacerbations.

44 patients had a raised serum IgE of ≥ 30 IU/ml. 30 of these patients reported frequent exacerbations, despite 16 of these patients taking systemic corticosteroids (potential criteria for therapy with anti-IgE).

37 patients consented to sputum induction and sufficient material for analysis was obtained in 24 of these patients. Cell differentiation showed an overwhelming neutrophilia with varying levels of macrophages and eosinophils within the samples (table 4).

**Table 4:** Cell differentiation of induced sputum (n = 24)

|  |  |  |  |
| --- | --- | --- | --- |
| Macrophages (%) | Neutrophils (%) | Lymphocytes (%) | Eosinophils (%) |
| 10.7 ± 0.5 | 80.6 ± 15.9 | 0.21 ± 0.5 | 5.5 ± 7.9 |

Figures denote mean ± SD values

Sputum eosinophilia of ≥ 2 % was found in 14/24 (58.3%) patients, with only 8 of these patients displaying blood eosinophilia of ≥ 150 cells/μl. 12 of these patients reported frequent exacerbations suggesting a tendency towards frequent exacerbation in the presence of sputum eosinophilia, however there was no significant difference in the exacerbation rates of the remaining patients without sputum eosinophilia. The correlation coefficient between blood and sputum eosinophilia was r =0.57, p = 0.0033 (figure 1). Routine sputum microbiology was examined in 47 patients with growth of a respiratory pathogen in 63.8% (30/47). 13 from 47 patients were on systemic corticosteroids.



**Figure 1:** Correlation between sputum eosinophilia and absolute blood eosinophilia, r = 0.57, p = 0.0033

A cluster analysis using the following variables: age, FEV1/FVC, FEV1 % predicted, smoking pack years, exacerbation rate, bronchodilator reversibility, serum IgE, absolute blood eosinophils and FeNO did not reveal clearly identifiable phenotypes of COPD. The exacerbation rate appears to relate positively with absolute serum eosinophilia using Pearson’s correlation coefficient (p < 0.05), but does not show a robust level of significance when the outliers are removed. Kendall’s rank correlation showed no significant correlation between exacerbation rate and serum eosinophilia (p = 0.7506) or FeNO (p = 0.7125) and a weak negative correlation between exacerbation rate and serum IgE (p = 0.0617)

Asthma-COPD Overlap (ACO)

12/80 (15%) patients met all the major criteria and at least one minor criterion for the diagnosis of ACO and these patients were compared to those with COPD alone (Table 5).

**Table 5:** Characteristics of ACO patients compared to COPD alone

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | Asthma-COPD Overlap (ACO)n =12 (%) | COPD Alonen = 68 (%) | p-value |
| Anthropomorphic dataAgeFemale sexBMI | 57 ± 5.79/12 (75%)24.5 ± 3.47 | 57.7 ± 5.0630/68 (44.2%)21.2 ± 3.1 | 0.850.0630.014 |
| Co-morbidityCVDDiabetesArterial hypertensionCHDHypercholesterolemia Cholesterol TG LDL HDL | 1/12 (8.33%)0/12 (0%)4/12 (33.3%)1/12 (8.33%)6/12 (50%) 247.3 ± 60.3 107.4 ± 48.2 146 ± 49 88.6 ± 20.3 | 1/68 (1.47%)2/68 (2.94%)30/68 (44.1%)30/68 (44.1%)22/68 (32.35%) 240.4 ±48.6 94.5 ± 44.4 152.2 ± 42.1 82.1 ± 19.7 | 0.160.5470.5430.01890.3260.3590.3610.8470.039 |
| InhaledCorticosteroids | 8/12 (66.6%) | 48/68 (70.6%) | 0.745 |
| Systemic therapyRoflumilastPrednisolonAzithromycinTheophyllin | 4/12 (33.3%)7/12 (58.3%)2/12 (16.67%)3/12 (25%) | 24/68 (35.3%)24/68 (35.3%)9/68 (13.2%)5/68 (7.4%) | 0.90.1980.6670.094 |
| Pulmonary rehabilitation within 3 years | 10/12 (83.3%) | 42/49 (85.7%) | 0.59 |
| Lung functionFEV1 (L)FEV1 (% pred)VC (%pred)TLC (% pred)DLCO (% pred) pO2 (mmHg)pCO2 (mmHg) | 0.52 ± 0.121.2 ± 4.6751.67 ± 13.2 135.67 ± 19.920.67 ± 7.349.4 ± 9.344.67 ± 7.63 | 0.63 ± 0.2121.1 ± 5.8149.0 ± 16.9140.1 ± 24.127.3 ± 13.252.6 ± 8.343.7 ± 6.5 | 0.1040.850.3380.4990.410.6170.925 |
| 6MWD (m) | 230.4 ± 106.4 | 250.2 ± 115.6 | 0.546 |
| Frequent exacerbationWith NIVWith ICU | 10/12 (83.3%)7/12 (58.3%)6/12 (50%) | 44/68 (64.7%)13/38 (34.2%)10/39 (25.6%) | 0.2610.004960.0368 |
| PHmPAP (mmHg) | 4/12 (33.3%)26.1 ± 12.1 | 17/55 (30.9%)23.1 ± 5.94 | 0.870.802 |
| Sputum bacteria | 5/8 (62.5%) | 25/39 (64.1%) | 0.93 |
| Blood eosinophils absolute (cells/µl) Blood or sputum eosinophilia ≥ 2% | 206.4 ± 155.68/12 (66.7%)  | 185.3 ± 161.340/68 (58.8%) | 0.70290.61 |

Figures denote mean ± SD values

CVD = cerebrovascular disease, CHD = coronary heart disease, TG = triglyceride, LDL = low density lipoprotein, HDL = high density lipoprotein, FEV1 = forced expiratory volume in 1 second, VC = vital capacity, RV = residual volume, TLC = total lung capacity, DLCO = diffusion capacity of the lung for carbon monoxide pO2 = partial pressure of oxygen, pCO2 = partial pressure of carbon dioxide, NIV = non-invasive ventilation, ICU = intensive care unit, PH = pulmonary hypertension, mPAP = mean pulmonary artery pressure

Patients with ACO had a significantly higher BMI (p = 0.014) and were less likely to suffer from CHD (p = 0.018). There were no significant differences in lung function or therapy in patients with ACO compared to those with COPD alone. The overall prevalence of pulmonary hypertension (defined as mean pulmonary arterial pressure (mPAP) of ≥ 25 mmHg at right heart catheter) was 31.8% (21/66) with a mean pulmonary artery pressure of 32±7mmHg. All patients had a lung perfusion scan and HRCT thorax with no evidence of pulmonary embolism or chronic thromboembolic pulmonary hypertension. There was no significant difference in the presence of pulmonary hypertension in patients with ACO compared to COPD alone and neither did it have a significant influence on the exacerbation rate. There was no significant difference between the mean blood eosinophil levels in patients with ACO compared to those with COPD alone, nevertheless the majority of patients with ACO (8/12) showed either serum or sputum eosinophil levels of ≥ 2%.

There appears to be more patients with frequent exacerbations in the group with ACO compared to COPD alone, however this difference was not statistically significant. Patients fulfilling the criteria for ACO reported significantly more severe exacerbations with the need for NIV or ICU (p < 0.05) than those with COPD alone.

**Discussion**

The studied group of COPD patients had severe airway obstruction with a mean FEV1 of less than 1 liter and marked hypoxemia. Data on diffusion capacity was limited due to the inability of patients to carry out the test, but nevertheless showed a severe reduction. Furthermore, the group had a considerable functional limitation as measured by the 6MWD. As most study patients enrolled were referred for evaluation for lung transplantation, this enabled a detailed examination of a group of patients with the severest form of the disease during a stable phase of their illness.

A large proportion of patients (67.5%) reported frequent exacerbations, despite intensive inhaled bronchodilator therapy often in combination with systemic corticosteroids, an oral phosphodiesterase 4 - (PDE4) inhibitor, or Azithromycin as well as recent in-patient cardio-pulmonary rehabilitation in more than half the group. This shows that there is a need for additional treatment in this group.

The key finding of this study is that patients fulfilling the criteria for ACO were significantly more likely to have more severe exacerbations, requiring the use of NIV or treatment on the ICU. This result supports the finding of recent studies, that these patients have more exacerbations and therefore potentially a more severe form of the disease [4,25].

We found a high percentage with self-reported history of atopy and an even higher number with evidence for allergen sensitization. Data on airflow reversibility following bronchodilator therapy shows only a small number of patients to have true reversibility with both a BDR of >12% as well as a rise of > 200ml. One weakness of this study is that the data on reversibility is incomplete. However, to some degree, reversibility is a well-known feature in both COPD and asthma and consequentially does not seem to be the most important factor in distinguishing ACO in patients with severe COPD. Additionally, it has been described that in cohorts with an FEV1 <1L, a BDR of 200ml is hard to achieve [25], once again diminishing the importance of reversibility in this cohort. It should however be noted, that regular inhaler therapy was not stopped prior to lung function testing and many patients were under treatment with systemic corticosteroids on top of dual or triple inhaled bronchodilator therapy, so that possibly a higher number of patients may have partially reversible expiratory airflow reduction.

As high eosinophil counts in COPD are a marker of Th2 response, these patients are also more likely to suffer from ACO. 58.7% of COPD patients showed a blood eosinophilia of ≥ 2% suggesting that this criterion is not suitable for use alone in differentiating an asthma phenotype of any clinical relevance.

The analysis of induced sputum in this study enabled a closer examination of the type of inflammation taking place in this cohort of patients with very severe COPD, which is not performed in routine clinical practice. The correlation between sputum and blood eosinophilia was moderate and comparable to previously known figures for correlation in this field [18,26]. There were however cases of severe sputum eosinophilia without a correlating serum eosinophilia, so that some cases of eosinophilic COPD may be missed, when looking at serum eosinophilia alone.

Generally, the number of patients with positive allergy tests and sputum and blood eosinophilia is high, despite the fact that a relevant number of patients were taking systemic corticosteroids.

Mild PH was commonly found at right-heart catheterization and is comparable to data known in this field [27,28].

COPD patients with asthma overlap features as well as relevant eosinophilia represent a treatable trait that may stand to benefit from targeted therapy. This study conducted a careful analysis of patients with severe COPD in a real-life setting and highlights a subgroup of patients with asthma features who are more at risk of severe exacerbation with all its known consequences; a group worthy of a potential trial with a rescue therapy with a biological agent and largely overseen in studies to date (the mean FEV1 was 1.2L in the phase 3 METREX and METREO trials testing Mepolizumab in eosinophilic COPD) [16].

**Conclusion**

Asthma features such as airway reversibility, allergen sensitization and blood and sputum eosinophilia are common findings in severe COPD patients but levels of clinical relevance need to be determined. Patients with ACO are more likely to have severe exacerbations despite optimal therapy. Given this, a future role for anti-IgE or anti-IL5 therapy needs to be considered in this group.

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