

Eosinophilia as a treatable trait in three patients with asthma and COPD

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Introduction

The combination of asthma and chronic obstructive pulmonary disease (COPD) in an individual can present significant challenges to achieving satisfactory outcomes. Recently, the concepts of precision medicine and treatable traits [1] have arisen as promising tools to improve the care of this group. In this series, we present three cases of patients with features of both asthma and COPD, in addition to peripheral blood eosinophilia. The novel implementation of personalized management using the treatable trait approach targeting eosinophilia resulted in significant benefits. These benefits included improvement in symptoms, lung function, and a marked decline in critical care admissions and exacerbation rates.

Case Series

Case 1

Case 1 is a 74-year-old male, ex-smoker with a previous diagnosis of COPD (see Table 1 for details). There was no history of childhood asthma or allergic disease. He had previously been maintained on 800/24 µg/day of budesonide/eformoterol and 5 µg/day of tiotropium.

Abstract

The combination of asthma and chronic obstructive pulmonary disease (COPD) in an individual can present significant challenges to achieving satisfactory outcomes. More recently, the concepts of precision medicine and treatable traits have arisen as promising tools to improve care for this group. In this series, we present three cases of patients with features of both asthma and COPD in addition to peripheral blood eosinophilia. The novel implementation of personalized management of the individual based on this treatable trait (eosinophilia) resulted in significant benefits. These benefits included improvement in symptoms, lung function, and a marked decline in critical care admissions and exacerbation rates.

In January 2017, he began to have recurring exacerbations. He presented to hospital on two separate occasions with acute exacerbations of COPD, and both times, peripheral blood eosinophils (PBE) were elevated at 0.5×10^9 cells/L and 0.6×10^9 cells/L, with baseline levels of 0.4×10^9 cells/L. Both exacerbations responded well to standard management. After his second exacerbation, a bronchoscopy was performed, and this demonstrated a cell count that was 72% eosinophils (Table 1).

Reversibility was first noted in March 2017, where he demonstrated a significant bronchodilator response to his forced expiratory volume in 1 s (FEV₁) of 520 mL, or 55%. In addition, there were no features of vasculitis or other diseases. At this point, he was started on prednisone of 15 mg/day in addition to maximal inhaler therapy to suppress his PBE count below 0.4×10^9 cells/L. He subsequently noticed considerable improvement to his symptoms and exercise tolerance (Table 2). In addition, his FEV₁ increased significantly from 0.54 to 2.27 L (Table 2). He has had no further exacerbations or hospitalizations at the time of writing (Table 2).

This is a dramatic outcome for this patient and demonstrates the importance of assessing inflammation and identifying treatable traits. It also highlights the difficulty, but

Table 1. Demographics and features of airways disease present in three patients with mixed asthma and chronic obstructive pulmonary disease.

Subject demographic	Case 1	Case 2	Case 3
Age (years)	73	68	74
Gender	Male	Male	Male
Asthma features	Eosinophilic bronchitis Allergic rhinitis BDR 520 mL, 55%	Childhood history of asthma Eosinophilic bronchitis FVC response to bronchodilator (370 mL, 12%)	FEV ₁ variability between visits 49% Eosinophilic bronchitis
COPD features	50 pack year ex-smoker DL _{CO} (HB corrected) 47% predicted	25 pack year ex-smoker DL _{CO} (HB corrected) 26% predicted Sputum microbiology <i>H. influenzae</i> and <i>Pseudomonas Aeruginosa</i>	38 pack year ex-smoker DL _{CO} (HB corrected) 48% predicted Sputum microbiology <i>H. influenzae</i>
Spirometry	Fixed, severe airflow obstruction FEV ₁ (L) 0.54 (18%) FVC (L) 1.15 (28%) FEV ₁ /FVC 0.47	Fixed, severe airflow obstruction 0.54 (17%) 2.59 (63%) 0.21	Fixed, severe airflow obstruction 1.23 (43%) 3.38 (85%) 0.36
CT findings	Evidence of emphysema, no other airway or parenchymal findings	Severe, predominantly upper lobe, centrilobular emphysema. Some parenchymal scarring at the lung bases and right middle lobe	Mild, bilateral upper lobe centrilobular emphysematous changes and evidence of mucus plugging in the lingular segment and right lower lobe. No bronchiectasis
Relevant comorbidities	Moderate obstructive sleep apnoea (treated with CPAP) GORD	Eczema GORD Anxiety/depression Vocal cord dysfunction	None
Bronchoscopy result	Histology: eosinophilic inflammatory infiltrate with a markedly thickened basement membrane and benign epithelium Bronchial lavage: eosinophils 72%, neutrophils 14% of total cell count (0.1 × 10 ⁶ cells/mL) Microbiology: only scant oropharyngeal flora	Histology: mild non-specific infiltrate of mixed inflammatory cells, including lymphocytes, rare neutrophils, and occasional eosinophils Bronchial lavage: eosinophils 15%, neutrophils 74% of total cell count (0.07 × 10 ⁶ cells/mL) Microbiology: occasional oropharyngeal flora	Not performed

BDR, bronchodilator response; CPAP, continuous positive airway pressure; CT, computed tomography; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; GORD, gastroesophageal reflux disease; HB, haemoglobin.

Table 2. Changes in objective health outcomes before and after initiation of targeted treatment towards peripheral blood eosinophilia with oral corticosteroids.

Case	Outcome	Pre OCS	Post OCS
1	<i>Pre-BD</i>		
	FEV ₁ (L)	N/A*	1.8 (71%)
	FVC (L)	N/A	2.89 (59%)
	FEV ₁ /FVC	N/A	0.62
	<i>Post-BD</i>		
	FEV ₁ (L)	0.54 (18%)	2.27 (74%)
	FVC (L)	1.15 (28%)	3.54 (87%)
	FEV ₁ /FVC	0.47	0.64
	DL _{CO} (% predicted)	47	N/A
	Exacerbation rate [†]	2	0 (4 months elapsed since initiation of OCS)
	Hospital admission rate [†]	2	0 (4 months elapsed since initiation of OCS)
	CAT score	26	11
6MWD (m)	343	520	
2	<i>Pre-BD</i>		
	FEV ₁ (L)	N/A*	0.69 (69%)
	FVC (L)	N/A	3.14 (82%)
	FEV ₁ /FVC	N/A	0.22
	<i>Post-BD</i>		
	FEV ₁ (L)	0.54 (17%)	0.74 (27%)
	FVC (L)	2.59 (63%)	3.51(92%)
	FEV ₁ /FVC	0.21	0.21
	DL _{CO} (% predicted)	N/A	35
	Exacerbation rate [†]	8	2
	Hospital admission rate [†]	8	0
	CAT score	28	5
6MWD (m)	256	466	
3	<i>Pre-BD</i>		
	FEV ₁ (L)	1.07 (37%)	1.91 (67%)
	FVC (L)	3.30 (83%)	2.75 (70%)
	FEV ₁ /FVC	0.32	0.69
	<i>Post-BD</i>		
	FEV ₁ (L)	1.23 (43%)	2.03 (71%)
	FVC (L)	3.38 (85%)	2.83 (72%)
	FEV ₁ /FVC	0.36	0.72
	DL _{CO} (% predicted)	N/A	N/A
	Exacerbation rate [†]	2	0 (9 months elapsed since initiation of OCS)
	Hospital admission rate [†]	1	0 (9 months elapsed since initiation of OCS)
	CAT score	24	16
6MWD (m)	50	505	

6MWD, 6 min walk distance; BD, bronchodilator; CAT, COPD Assessment test; COPD, chronic obstructive pulmonary disease; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; N/A, not available; OCS, oral corticosteroids.

*Not available as patient had taken short-acting bronchodilator prior to testing.

†Rates measured per 12-month period before versus after initiation of chronic maintenance oral corticosteroid, except where indicated.

necessity, of recognizing adult onset asthma in the shadow of established COPD and a significant smoking history [2]. His impressive response to prednisone highlights the

importance of using the identified treatable target of eosinophilia in this patient to realize improved health outcomes for him.

Case 2

This case is of a 68-year-old male with a childhood history of asthma. He was also an ex-smoker with fixed airflow obstruction and emphysema (Table 1). He was GOLD stage 4, group D after completion of pulmonary rehabilitation in 2015 and was optimized on 1000/100 µg/day of fluticasone/salmeterol, 18 µg/day of tiotropium, and Azithromycin 250 mg daily due to recurrent exacerbations.

In 2015, he suffered a series of acute exacerbations. Two were admissions with hypercapnoeic respiratory failure requiring non-invasive ventilation, with one complicated by a pneumothorax and need for intubation and mechanical ventilation. His exacerbation frequency increased from every 3 months to monthly by September 2015, totalling six incidents for that calendar year. These were associated with PBE counts from 0.1 to 1.1×10^9 cells/L. Bronchoscopy confirmed airway eosinophilia of 15% of the total cell count (Table 1).

In April 2016, he was started on regular prednisone at 15 mg daily with the aim of suppressing his PBE count $< 0.4 \times 10^9$ cells/L. Since doing so, the patient has noticed improvement in his COPD Assessment Test (CAT) score from 28 to 5, and he has gone from experiencing eight exacerbations per year prior to starting regular prednisone to two exacerbations per year afterwards (none needing admission). He has been able to wean down from 10 mg/day of prednisone to 5 mg/day to continue to suppress his PBE count to $< 0.3 \times 10^9$ cells/L. He has improved his quality of life, and his symptomatic benefit has allowed him to continue with pulmonary rehabilitation (Table 2). We believe this to be attributable to better recognition of asthma as a concomitant feature of his respiratory disease, in addition to COPD, and the targeted therapy of his eosinophilia as a treatable trait.

Case 3

This case is of a 74-year-old male ex-smoker with a history of COPD (Table 1). He had previously been maintained on 800/24 µg/day of budesonide/formoterol and 18 µg/day of Tiotropium.

He had two exacerbations starting in July 2015 demonstrating PBE of 0.9×10^9 cells/L and 0.6×10^9 cells/L. Following the cessation of beta blocker therapy, his FEV₁ improved from 1.17 (42% predicted) to 2.03 L (70%). Despite this and the addition of 320 µg/day of inhaled ciclesonide, he continued to demonstrate excessive variability in his FEV₁ (Table 1).

Recognition of excessive variability to his airflow obstruction and eosinophilia, and the exclusion of other contributory diagnoses, led to the initiation of maintenance prednisone at 10 mg daily in October 2016. This led

to reduced variability of his FEV₁, improved exercise tolerance, and decreased shortness of breath and cough with treatment. In addition, he has had no further exacerbations. The prednisone dose is being slowly reduced to keep the PBE count $< 0.4 \times 10^9$ cells/L. Thus, by recognizing the asthma component to his airways disease and targeting the eosinophilic trait of his COPD and asthma overlap, the patient was able to realize these benefits.

Discussion

As seen in all three of these cases, the identification of eosinophilia as a treatable trait has allowed for real-world targeted therapy to improve outcomes for each individual. This is consistent with our current knowledge of the role of the eosinophil in obstructive lung disease once other causes of eosinophilia have been ruled out. Eosinophilia in COPD or asthma is associated with an increased risk of exacerbations [3,4]. A management strategy based on modulating PBE or sputum eosinophilia has been shown to reduce exacerbation frequency in COPD [4] and in asthma [5–7]. It would follow that the management of complex obstructive lung disease by titrating corticosteroid dose based on PBE count should similarly lead to improved outcomes, as it has in these cases.

Long-term use of systemic corticosteroids, however, is associated with serious side effects [8]. Importantly, we are not advocating for their indiscriminate regular use in those with frequent exacerbations. In this series, these individuals were faced with dramatically worsening and life-threatening disease, and the targeted use of prednisone has stabilized this, preventing or at least reducing the severity of further exacerbations; reducing the number of days spent on high-dose corticosteroid; and allowing other effective treatments, like pulmonary rehabilitation, to be applied. While adverse events were not identified in these three cases, where possible, the ultimate goal should be to effect control of disease on the lowest possible dose of corticosteroid. The duration of treatment is uncertain in this population, but ultimately, the discontinuation of oral corticosteroids would be the ideal goal. Anti-interleukin 5 (anti-IL5) treatment has been shown to improve exacerbations in this population, and may be preferable due to less potential toxicity, but remains to be further studied and implemented as an alternative treatment [9,10].

Generally, studies exclude patients where these diseases overlap, leaving little evidence in those patients with both asthma and COPD. What we do know is that eosinophilia is associated with a more rapid decline in FEV₁, increased exacerbation risk, and increased mortality in asthma or COPD [11,12]. The targeting of this treatable trait in a population with mixed obstructive airways disease should, as a result, also lead to improved outcomes, as it has here.

This relationship between asthma and COPD is a controversial subject. Clinicians recognize that, in many patients, there is considerable overlap despite distinct management strategies in guidelines. An attempt to reconcile this has resulted in labelling patients as having Asthma-COPD Overlap Syndrome (ACOS). Unfortunately, there is no consensus in defining ACOS nor a clear view as to how it will impact prognosis or management [13]. In contrast there have been major advances in our understanding of both asthma and COPD. Anderson has described the need to think of complex airways disease as endotypes, defined either functionally or pathologically by a mechanism or treatment response [14]. This allows us to focus on the components of chronic airways disease in individuals and identify treatable traits [1]. In the era of precision medicine, targeting treatable traits in chronic airways disease should lead to better targeted therapy, with fewer side effects and better outcomes [1]. The key to this approach, for the clinician, is to be able to identify an endotype, with a biomarker that is reliable and easily measurable, and a treatment that is effective as opposed to fixating on disease labels [15]. We propose that eosinophilic airway inflammation is such an endotype.

There has, thus far, been limited publication on the application of this evidence to treatment [16]. A pilot study by McDonald identified that specifically targeting and managing airway eosinophilia in a COPD cohort resulted in reduced airway eosinophilia and better health-related quality of life [16]. Table 2 demonstrates that considerable improvement to outcomes can be achieved when using this approach in a population with both asthma and COPD. While simple in theory, the consistent application of this concept in practice remains to be standardized.

In summary, this case series demonstrates the ability to apply the concept of the treatable trait to the complex population of patients with both asthma and COPD. Importantly, this highlights the need to see through the labels of these diseases to the individual traits that reflect therapeutic targets. By using this novel and targeted treatable trait framework, we can focus on specific therapies for our patients, reducing exacerbation risk and improving lung function, symptoms, and quality of life, as seen in this group, while also reducing superfluous medications and side effects. The next step will be to build the tools to standardize implementation of what we know about these endotypes and treatable traits and bring precision medicine from trials to patients in real-world clinics.

Disclosure statement

Appropriate written informed consent was obtained for the publication of this case series and accompanying images.

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