



# Precision medicine in COPD: review of mepolizumab for eosinophilic COPD

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## Journal club

### Commentary on:

Pavord ID, *et al.* Mepolizumab for eosinophilic chronic obstructive pulmonary disease. *N Engl J Med* 2017; 377: 1613–1629.

## Introduction

Precision medicine for chronic obstructive pulmonary disease (COPD) can improve management for those who may have otherwise exhausted conventional therapy. Approximately 40% of patients with COPD have a persistently elevated blood eosinophil count  $\geq 150$  cells  $\mu\text{L}^{-1}$  [1]. Blood eosinophils are reflective of sputum eosinophil count, which is used as a marker of eosinophilic airway inflammation [2, 3]. Debatably, raised blood eosinophils identify a distinct COPD phenotype with increased frequency and severity of exacerbations [4–6]. Guiding corticosteroid treatment according to the level of blood eosinophils results in a reduction in exacerbations, which is indicative of its value as a biomarker of corticosteroid responsiveness [7–9]. However, the use of inhaled corticosteroids has been associated with increased risk of pneumonia [10, 11].

Previous studies have investigated the potential for targeted monoclonal antibody therapy for COPD. BRIGHTLING *et al.* [12] studied benralizumab, an interleukin (IL)-5 receptor antibody. IL-5 stimulates growth, maturation and release of eosinophils and precipitates their survival to allow ongoing inflammatory response. *Post hoc* analysis comparing the effects of benralizumab on a subgroup of patients with raised blood eosinophils found a significant improvement in lung function, but no effect on exacerbation rate [12].

Mepolizumab is a monoclonal antibody to IL-5. Mepolizumab has been well documented to reduce eosinophilic inflammation and exacerbations in severe asthmatic patients with raised blood and sputum eosinophils [13–15]. To this end, PAVORD *et al.* [16] explored the impact of mepolizumab on frequently exacerbating COPD patients, on maximal triple inhaled therapy, with raised blood eosinophils. Here, we analyse the study and findings, and its impact on clinical practice.

## Study design

The study by PAVORD *et al.* [16] was constructed into two multicentre, phase 3, randomised,



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**Mepolizumab can reduce exacerbation rates in those with frequently exacerbating, severe COPD and raised blood eosinophils; this represents a further advance in precision medicine for COPD and targeted therapies** <http://ow.ly/uklu30m4YcU>



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placebo-controlled, double-blind, parallel-group trials: mepolizumab *versus* placebo as add-on treatment for frequently exacerbating COPD patients (METREX), and mepolizumab *versus* placebo as add-on treatment for frequently exacerbating COPD patients characterised by eosinophil level (METREO). Table 1 summarises the key study characteristics and methods.

Patients were aged  $\geq 40$  years with at least a 1-year diagnosis of COPD, taking maximal triple inhaled therapy, and who had a history of two or more moderate exacerbations (treated with systemic

**Table 1** Key study characteristics and methods

Characteristic	METREX	METREO	
<b>Population</b>	All patients receiving $\geq 1$ dose of mepolizumab or placebo	Patients with blood eosinophils $\geq 150$ cells· $\mu\text{L}^{-1}$ at screening or $\geq 300$ cells· $\mu\text{L}^{-1}$	Patients with blood eosinophils $\geq 150$ cells· $\mu\text{L}^{-1}$ at screening or $\geq 300$ cells· $\mu\text{L}^{-1}$
<b>Intervention 1</b>	Mepolizumab 100 mg s.c. (n=417)	Mepolizumab 100 mg s.c. (n=233)	Mepolizumab 100 mg s.c. (n=223)
<b>Intervention 2</b>			Mepolizumab 300 mg s.c. (n=225)
<b>Control</b>	Placebo (0.9% saline) s.c. (n=419)	Placebo (0.9% saline) s.c. (n=229)	Placebo (0.9% saline) s.c. (n=226)
<b>Key inclusion criteria</b>	COPD diagnosis: history of COPD for $\geq 1$ year in accordance with the definition provided by the American Thoracic Society/European Respiratory Society [17] FEV <sub>1</sub> to FVC ratio $< 0.70$ before and after bronchodilator use and a post-bronchodilator FEV <sub>1</sub> $> 20\%$ and $\leq 80\%$ of the predicted value $\geq 2$ moderate COPD exacerbations (use of systemic corticosteroids and/or treatment with antibiotics) or $\geq 1$ severe COPD exacerbation (required hospitalisation) Triple inhaled therapy for at least 12 months prior to screening including 3 months of an ICS at dose $\geq 500$ $\mu\text{g}\cdot\text{day}^{-1}$ fluticasone propionate dose equivalent, plus LABA and LAMA; or must be taking for 12 months prior to screening (but not in 3 months immediately prior) ICS plus LABA or LAMA and a phosphodiesterase-4 inhibitor, methylxanthine, or a combination of short-acting $\beta_2$ -agonist and short-acting muscarinic antagonist $\geq 40$ years of age at screening Confirmed COPD with no restrictions on smoking status (smoker, nonsmoker, never-smoker)		
<b>Key exclusion criteria</b>	Current diagnosis of asthma Previous history of asthma in never-smokers Other respiratory disorders, including $\alpha_1$ -antitrypsin deficiency, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, primary pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases Pneumonia, exacerbation, lower respiratory tract infection within 4 weeks prior to screening Other conditions causing elevated eosinophils or parasitic infection		
<b>Randomisation</b>	Computer-generated, permuted block		
<b>Analysis</b>	Intention-to-treat		
<b>Primary end-point</b>	Yearly rate of moderate to severe exacerbations		
<b>Secondary end-points</b>	Time to first exacerbation Emergency department visits Hospitalisation Average yearly change in St George's Respiratory Questionnaire score Average yearly change in COPD Assessment Test score		
<b>Pre-specified meta-analysis</b>	Blood eosinophil stratification based on the following thresholds: $< 150$ and a history of $\geq 300$ cells· $\mu\text{L}^{-1}$ in the previous year; $\geq 150$ to $< 300$ cells· $\mu\text{L}^{-1}$ ; $\geq 300$ to $< 500$ cells· $\mu\text{L}^{-1}$ ; and $\geq 500$ cells· $\mu\text{L}^{-1}$		
<b>Post hoc meta-analysis</b>	Blood eosinophils $< 150$ cells· $\mu\text{L}^{-1}$ , blood eosinophils $\geq 300$ cells· $\mu\text{L}^{-1}$ Effect of mepolizumab compared to placebo on moderate/severe exacerbations treated with glucocorticoids (alone or in addition to antibiotics), or those treated with antibiotics alone		

FEV<sub>1</sub>: forced expiratory volume in 1 s; FVC: forced vital capacity; ICS: inhaled corticosteroid; LABA: long-acting  $\beta_2$ -agonist; LAMA: long-acting muscarinic-receptor antagonist.

glucocorticoids, antibiotics or both) or one or more severe exacerbation (hospitalisation). Those with a history of asthma were excluded. Smoking status and pack-years were not part of the inclusion criteria. In METREX, patients were randomised 1:1 to receive subcutaneous injections of either mepolizumab 100 mg or placebo (0.9% saline), while in METREO patients were randomised 1:1:1 to receive either mepolizumab 100 mg, mepolizumab 300 mg or placebo (0.9% saline) every 4 weeks for 52 weeks.

METREX patients were stratified by blood eosinophils at screening visit: either  $\geq 150$  cells· $\mu\text{L}^{-1}$ ,  $\geq 300$  cells· $\mu\text{L}^{-1}$  at any point in the previous year, or those who were non-eosinophilic ( $< 150$  cells· $\mu\text{L}^{-1}$ ); while METREO included only those with an eosinophilic phenotype. The primary end-point of both trials was yearly rate of moderate or severe exacerbations. Secondary end-points were time to first exacerbation, emergency department visits, hospitalisation, and average yearly changes in St George's Respiratory Questionnaire and COPD Assessment Test scores. Results were controlled for smoking status, number of exacerbations in the previous year, baseline disease severity (percentage of predicted FEV<sub>1</sub>) and geographic region.

## Key results

### METREX

836 patients were analysed according to an intention-to-treat analysis. 94% or more patients were Global Initiative for Chronic Obstructive Lung Disease (GOLD) group D COPD ( $\geq 2$  exacerbations in total,  $\geq 1$  leading to hospitalisation, and either a Medical Research Council dyspnoea scale score of  $\geq 2$  or a COPD Assessment Test score of  $\geq 10$ ). There was a significant difference in annual exacerbation rates in those with an eosinophilic phenotype ( $\geq 150$  cells· $\mu\text{L}^{-1}$  at screening visit or  $\geq 300$  cells· $\mu\text{L}^{-1}$  at any point in the previous year) between the mepolizumab groups and placebo groups (rate ratio 0.82, 95% CI 0.68–0.98;  $p=0.04$ ). In the undifferentiated population there was no significant difference in exacerbation rates between mepolizumab and placebo (1.49 versus 1.52 per year, respectively). Regarding secondary end-points, those with an eosinophilic phenotype had a significantly increased time to exacerbation (hazard ratio 0.75, 95% CI 0.60–0.94;  $p=0.04$ ), but there was no significant difference in the undifferentiated population. A pre-specified meta-analysis was performed by stratifying screening blood eosinophil count as follows:  $< 150$  and a history of  $\geq 300$  cells· $\mu\text{L}^{-1}$  in the previous year;  $\geq 150$  to  $< 300$  cells· $\mu\text{L}^{-1}$ ;  $\geq 300$  to  $< 500$  cells· $\mu\text{L}^{-1}$ ; and  $\geq 500$  cells· $\mu\text{L}^{-1}$ . Patients with higher blood eosinophil count had a greater benefit from mepolizumab. In particular, in those with blood eosinophils  $\geq 300$  cells· $\mu\text{L}^{-1}$ , the exacerbation rate was 23% lower in those treated with mepolizumab than placebo.

### METREO

674 were included in the intention-to-treat protocol. Patients received mepolizumab at 100 mg (low dose), mepolizumab at 300 mg (high dose) or a placebo, with the primary aim of determining optimal dosing of mepolizumab. Similarly, 94% or more patients were GOLD group D COPD patients. METREO did not show any significant benefit from high-dose mepolizumab compared to low-dose mepolizumab in eosinophilic patients.

### Safety

The most commonly reported side-effects were exacerbations or worsening of COPD, nasopharyngitis, headache and pneumonia. While METREX and METREO had 4% and 3% mortality rates, respectively, rates were comparable with the placebo group. Similarly, there was no significant difference in systemic reaction, injection site reaction or event leading to treatment discontinuation between the groups in either trial.

## Strengths and limitations

These were the largest trials of targeted IL-5 therapy in COPD. METREX and METREO set out to ask the specific question of whether mepolizumab can reduce the rate of exacerbations in patients with severe COPD. PAVORD *et al.* [16] have highlighted a population of COPD patients that may specifically benefit from targeted therapy in this form, namely those with raised blood eosinophils who have a high rate of exacerbations despite maximal standard therapy. These studies showed that patients with high blood eosinophils in the context of severe COPD with frequent exacerbations benefit from a 4-weekly 100-mg subcutaneous injection of mepolizumab. This benefit is realised in terms of reduced exacerbation rate and time to next exacerbation. Despite this, lung volumes and quality of life indices were not significantly altered. Although mortality was only measured as part of a composite end-point (*i.e.* COPD exacerbations), the death rate was low overall and broadly comparable between groups.

Prior to METREX/METREO, BRIGHTLING *et al.* [12] reported hopeful results on the use of benralizumab, an IL-5 receptor monoclonal antibody, in COPD patients with raised blood eosinophils. They experienced a significant improvement in lung function, albeit with no change in exacerbation rate. The discrepancy in results between mepolizumab and benralizumab is most likely due to differences in trial population. The benralizumab trial population had fewer exacerbations at baseline, had slightly less severe COPD, and included only current smokers or ex-smokers. Similarly, the difference in trial populations may explain why those in the benralizumab trial experienced a significant improvement in pre-bronchodilator FEV<sub>1</sub>, unlike

with mepolizumab. Interestingly, this may reflect an important relationship between smoking status, blood eosinophils and treatment response.

This study by PAVORD *et al.* [16] relies upon stratifying patients by blood eosinophil level at a single time point. This strategy is clinically feasible and applicable to practical medicine. Blood eosinophil levels have been previously demonstrated to be stable over time: SOUTHWORTH *et al.* [18] showed that >80% of patients using the blood eosinophil cut-off of 150 cells· $\mu\text{L}^{-1}$  will remain either eosinophilic or non-eosinophilic after 6 months or 2 years, suggesting that blood eosinophil level is a stable marker of phenotype.

In these two trials, the incidence of pneumonia was higher (9–11%) than in other trials involving a similar cohort of COPD patients (2–7%) [11]. The authors posit that this may be due to all patients taking inhaled corticosteroids. There was no statistically significant difference in the incidence of

pneumonia between the mepolizumab and placebo groups in both trials. This potentially highlights the need for steroid-sparing agents in the treatment of COPD.

## Conclusion

Mepolizumab benefits patients with severe, treatment-resistant COPD who frequently exacerbate and have raised blood eosinophil levels, to reduce the rate of exacerbations and time to next exacerbation. The treatment effect increases with increasing baseline blood eosinophil level. Despite the heterogeneity of COPD, this study draws attention to a phenotype based solely on blood eosinophils, which may benefit from personalised treatment when standard therapies fall short. Further research harnessing the ideals of precision medicine may lead to further unique pathways and a potential agent to replace corticosteroids.

## Conflict of interest

None declared.

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