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SHORT COMMUNICATION

Is Blood Eosinophil Count a Predictor of Response to Bronchodilators in Chronic Obstructive Pulmonary Disease? Results from Post Hoc Subgroup Analyses

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Abstract

Background Chronic obstructive pulmonary disease (COPD) patients with blood eosinophil (EOS) count ≥2 % benefit from exacerbation reductions with inhaled corticosteroids (ICSs). We conducted post hoc analyses to determine if EOS count ≥2 % is a marker for greater responsiveness to the bronchodilators umeclidinium (UMEC; long-acting muscarinic antagonist), vilanterol (VI; long-acting β_2-agonist) or UMEC/VI combination.

Methods Effects of once-daily UMEC/VI 62.5/25, UMEC 62.5 and VI 25 μg versus placebo on trough forced expiratory volume in one second (FEV_1), Transition Dyspnoea Index (TDI), St George's Respiratory Questionnaire (SGRQ) scores and adverse event (AE) incidences in four completed, 6-month studies were assessed by EOS subgroup. Trough FEV_1 was also evaluated by ICS use and EOS subgroup. Analyses were performed using a repeated measures model.

Results At baseline, 2437 of 4647 (52 %) patients had EOS count ≥2 %. Overall, ≈50 % of patients used ICSs. At day 169, no notable variations were observed in trough FEV_1 least squares mean differences between EOS subgroups versus placebo for UMEC/VI, UMEC and VI; results according to ICS use were similar. No differences were reported between EOS subgroups in TDI and SGRQ scores on day 168, or for incidences of AEs, serious AEs and AEs leading to withdrawal.

Conclusions Response to UMEC/VI, UMEC and VI in terms of trough FEV_1, dyspnoea and health-related quality of life was similar for COPD patients with baseline EOS counts ≥2 or <2 %. EOS count did not appear to predict bronchodilator response in either ICS users or non-users.

Key Points

Response, as assessed by trough forced expiratory volume in 1 s, dyspnoea and health-related quality of life, to treatment with once-daily umeclidinium (UMEC)/vilanterol (VI) (62.5/25 μg), UMEC (62.5 μg) or VI (25 μg) was similar in chronic obstructive pulmonary disease patients with eosinophil (EOS) counts <2 or ≥2 % at baseline.

EOS count does not appear to predict bronchodilator response in either inhaled corticosteroid users or non-users.

No notable differences were observed between EOS subgroups in the incidence of adverse events (AEs), serious AEs or AEs leading to withdrawal

Ahmar Iqbal was employed by GSK at the time of the study.

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1 Introduction

Eosinophilic airway inflammation, which can increase during exacerbations, occurs in some patients with chronic obstructive pulmonary disease (COPD) [1]. It has been suggested that a biomarker for such inflammation is blood eosinophil (EOS) count [2] and that an EOS count of ≥2 % may be associated with an increased COPD exacerbation risk [3]. This EOS cut-off may identify patients who would benefit from exacerbation reduction with inhaled corticosteroids (ICSs) [4, 5]. Pascoe et al. [5] investigated different EOS cut-offs and found 2 % to be the most appropriate.

A question of interest is whether a blood EOS count of ≥2 % is a marker of patients who are responsive not only to ICSs but also to bronchodilators. We conducted post hoc analyses to determine if EOS count ≥2 % is a marker for greater responsiveness to bronchodilator treatment with umeclidinium [UMEC; long-acting muscarinic antagonist (LAMA)], vilanterol [VI; long-acting β_2 agonist (LABA)] and UMEC/VI.

2 Methods

Details of the four 24-week, multicentre, randomised, placebo- or active-controlled studies are published (Clinicaltrials.gov identifiers: NCT01313637, NCT01313650, NCT01316900, NCT01316913) [6–8]. Key inclusion criteria were males and females (≥40 years) with COPD; current or former cigarette smokers (≥10 pack-year smoking history); post-salbutamol forced expiratory volume in 1 s (FEV_1)/forced vital capacity <0.7 and predicted FEV_1 ≤70 % of normal; and a modified Medical Research Council dyspnoea score ≥2 [6–8].

In study NCT01313637,[1] 1493 patients were randomised 3:3:3:2 to UMEC/VI 125/25 (delivering 113/22 μg), UMEC 125, VI 25 μg or placebo, respectively [6]. In study NCT01313650, 1532 patients were randomised 3:3:3:2 to UMEC/VI 62.5/25 μg (delivering 55/22 μg), UMEC 62.5, VI 25 μg or placebo, respectively [7]. In studies NCT01316900 and NCT01316913, 2332 patients were randomized 1:1:1:1 to UMEC/VI 125/25, UMEC/VI 62.5/25 μg, tiotropium bromide 18 μg, and either VI 25 or UMEC 125 μg, respectively [8]. Once-daily treatments were administered using the ELLIPTA® dry powder inhaler[2] except for tiotropium (administered via the Handihaler®).

Post hoc subgroup analyses used integrated data ($n = 4713$) from the intent-to-treat (ITT) populations in these studies, excluding one site due to Good Clinical Practice (GCP) violations. Subgroups were defined by EOS category (<2 or ≥2 %) at baseline. As patients could take a concurrent stable dose of an ICS throughout these studies, additional subgroups were defined according to ICS use at screening and baseline EOS category. Trough FEV_1 (primary efficacy endpoint in each study), Transition Dyspnoea Index (TDI) focal score and St George's Respiratory Questionnaire (SGRQ) total score were analysed using a repeated measures model [terms: study, treatment, smoking status at screening, baseline or Baseline Dyspnea Index (BDI), day, geographical region, EOS subgroup, and day by baseline/BDI, day by treatment, EOS subgroup by treatment, and EOS subgroup by day by treatment interactions]. Trough FEV_1 was also analysed by additional EOS subgroups of <4 or ≥4, <6 or ≥6, and <2 %, 2 to <4, 4 to <6 or ≥6 % (using the same model), and by EOS category and ICS use, using the same model but using the 4-level ICS/EOS subgroup instead of EOS subgroup. Adverse events (AEs), serious AEs (SAEs) and AEs leading to withdrawal were summarised by EOS category. Data are presented for UMEC/VI 62.5/25 and UMEC 62.5 μg (both approved doses), and VI 25 μg.

3 Results

At baseline, 2210 of 4647 (48 %) and 2437 of 4647 (52 %) patients had EOS counts <2 and ≥2 %, respectively. Across treatments, the proportion of patients with EOS count ≥2 % was similar (49–55 %). Approximately 50 % of all patients were ICS users. The overall proportion of patients with EOS ≥2 % was 53 % (47–61 % across treatments) for ICS users, and 52 % (49–53 %) for non-ICS users.

For the overall ITT populations, patient demographics and disease characteristics (Electronic Supplementary Material Table S1) for each treatment (data not shown) were well matched between EOS subgroups.

In the EOS <2 and ≥2 % subgroups, trough FEV_1 was statistically significantly increased by UMEC/VI, UMEC and VI versus placebo at all timepoints ($p < 0.001$; Fig. 1a–c). There were no differences between the EOS <2 and ≥2 % subgroups in trough FEV_1 least squares (LS) mean differences from placebo for UMEC/VI, UMEC and VI treatments (Fig. 1a–c). The LS mean differences (95 % confidence interval) from placebo for EOS <2 versus ≥2 %, respectively, at day 169 were 197 (155–238) versus 205 mL (166–245) with UMEC/VI; 139 (89–189) versus 130 mL (83–176) with UMEC; and 109 (69–150) versus 100 mL (62–138) with VI. Results for EOS subgroups using different cut-offs were very similar to those using the 2 % cut-off (data not shown). The trough FEV_1 results with

[1] The doses of UMEC used in this study (UMEC/VI 125/25 μg, UMEC 125 μg) are not approved.

[2] ELLIPTA® is a trademark of the GSK group of companies.

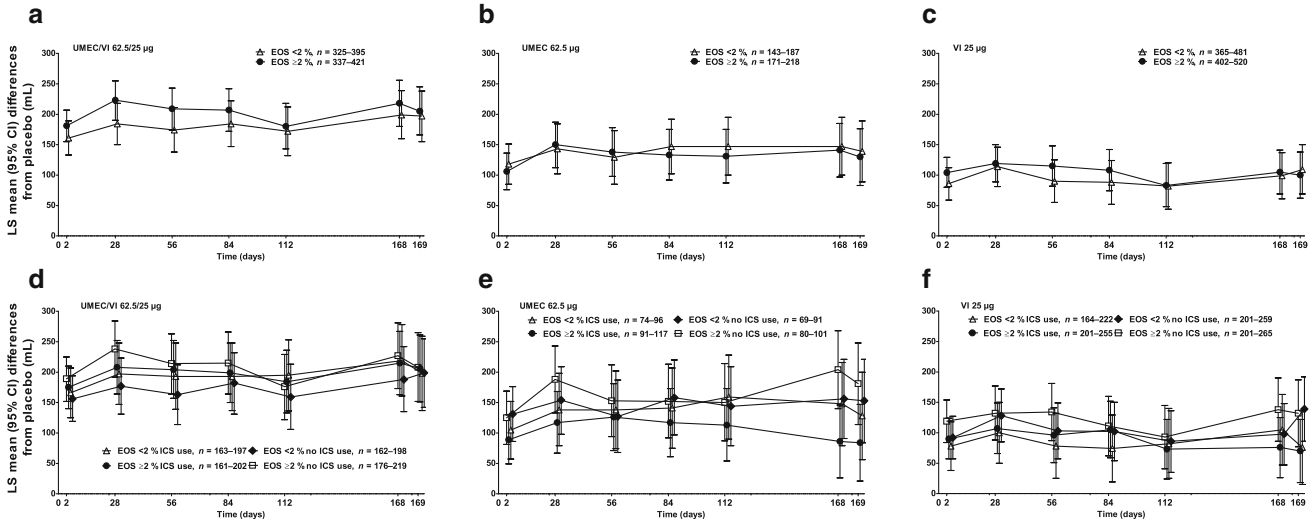

Fig. 1 Least squares mean differences from placebo in trough force expiratory volume at 1 s (at various timepoints) with umeclidinium/vilanterol, umeclidinium and vilanterol treatment, by baseline eosinophil subgroup (**a**–**c**), and by baseline eosinophil subgroup and concomitant inhaled corticosteroid use (**d**–**f**). *CI* confidence interval, *EOS* eosinophil, *ICS* inhaled corticosteroid, *LS* least squares, *UMEC* umeclidinium, *VI* vilanterol

UMEC and VI in patients with baseline EOS counts <2 or ≥2 % were more variable in ICS users and non-users than in the overall population (Fig. 1d–f).

There were no differences in the LS mean difference from placebo in TDI focal score or SGRQ total score between EOS <2 and ≥2 % subgroups for UMEC/VI, UMEC and VI treatments at day 168 (Electronic Supplementary Material Table S2), or at any other timepoints evaluated (data not shown).

For the EOS <2 and ≥2 % subgroups, respectively, the incidences of AEs were 49–56 and 46–55 %, SAEs were 3–7 and 4–7 %, and AEs leading to withdrawal were 4–8 and 4–7 % across treatment groups.

4 Discussion

Our retrospective analyses of a large dataset demonstrate that the response [assessed by trough FEV_1, dyspnoea and health-related quality of life (HR-QOL)] to treatment with once-daily UMEC/VI (62.5/25 µg), UMEC (62.5 µg) or VI (25 µg) was similar in COPD patients with EOS counts <2 or ≥2 % at baseline. In addition, the EOS count does not appear to predict bronchodilator response in either ICS users or non-users. Moreover, no remarkable differences in the incidence of AEs, SAEs or AEs leading to withdrawal were observed between EOS subgroups.

Our findings with UMEC and VI are in contrast to results with corticosteroids in COPD patients. For example, an EOS cut-off of ≥2 % was identified as a potential biomarker to guide whether oral corticosteroid therapy was required to prevent COPD exacerbations [4]. With the ICS/LABA combination of fluticasone furoate/VI, COPD exacerbations were significantly reduced by 29 % ($p < 0.001$) in the EOS count ≥2 % subgroup, but only by 10 % ($p = 0.283$) in the EOS count <2 % subgroup [5]. This is supported by the randomised, double-blind, parallel-group FORWARD (FOsteR 48-week trial to reduce exAceRbations in COPD) study, which reported that increasing blood EOS count was associated with a greater reduction in exacerbations when beclomethasone dipropionate was added to formoterol fumarate in patients with severe COPD and a history of exacerbations [9]. This differential response is perhaps unsurprising given that corticosteroids act as anti-inflammatory agents in COPD and EOS are a corticosteroid-responsive cell type [10], while, in contrast, LABAs and LAMAs act as bronchodilators via stimulation of adrenergic receptors or inhibition of muscarinic receptors, respectively [11], although LAMAs have some anti-inflammatory properties [12]. Biomarkers have great potential to improve decision making in COPD. Our results suggest that EOS will not be of value in making decisions about bronchodilator use; however, these findings need to be confirmed in prospective studies.

5 Conclusion

Response to UMEC/VI, UMEC and VI in terms of trough FEV_1, dyspnoea and HR-QOL was similar for COPD patients with EOS counts ≥2 or <2 % at baseline. EOS

count did not appear to predict bronchodilator response in either ICS users or non-users.

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Compliance with Ethical Standards

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Conflict of interest AI, NCB and JB are employees of GSK and hold stock in GSK.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent All patients gave their written informed consent prior to the start of each study.

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