Blood eosinophils and treatment response with triple and dual combination therapy in COPD: analysis of the IMPACT trial

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RESEARCH IN CONTEXT

Evidence before this study

Inhaled corticosteroids (ICS)-containing therapies reduce exacerbation rates in patients with chronic obstructive pulmonary disease (COPD). Studies have demonstrated that higher blood eosinophil counts are associated with a greater treatment benefit with ICS. Studies that have investigated the association between blood eosinophil counts and response to ICS-containing therapy in COPD, published from 2008 onwards, were identified from PubMed, using the search terms: "inhaled corticosteroids", "blood eosinophil count", "exacerbation", and "COPD". The relationship between ICS and blood eosinophil count has been modelled in various post hoc analyses, with the greatest effects of ICS on reduction of COPD exacerbations shown at higher eosinophil levels. The majority of these analyses have focused on the response to ICS/long-acting β_2-agonist (LABA) versus LABA using dichotomised eosinophil counts. However, additional evidence is required to understand the relationship between blood eosinophil count and the effect of ICS as a continuum with both single-inhaler triple therapy (SITT) and dual inhaled therapies, and to determine whether this relationship is modified by other factors known to modulate ICS effects, such as cigarette smoking.

Added value of this study

The large size of the population in the recent IMPACT trial, which compared once-daily SITT (fluticasone furoate/umeclidinium/vilanterol [FF/UMEC/VI]) with dual inhaled therapy (FF/VI and UMEC/VI), allows modelling of the relationship between baseline blood eosinophil count and the effect of ICS as a continuum on COPD exacerbations and other outcomes. These analyses demonstrated greater ICS treatment effects were associated with increasing blood eosinophil counts. This was seen in both former and current smokers with larger benefit seen in former smokers.

Implications of all the available evidence

This is the first analysis using data modelling of SITT or ICS/LABA versus LAMA/LABA to demonstrate that, in a high exacerbation risk population, the response to ICS-containing therapy can be predicted using blood eosinophil counts and smoking status. The continuous nature of the relationship between increasing blood eosinophil count and reduction in exacerbations with use of ICS is clearly demonstrated. Assessment of blood eosinophils should, therefore, be used as part of a precision medicine approach to optimise the use of ICS within combination therapies in patients with COPD.

ABSTRACT

Background: Previous studies highlighted a relationship between reduction in exacerbation rates with inhaled corticosteroid (ICS)-containing therapies and baseline blood eosinophil count in chronic obstructive pulmonary disease (COPD). The IMPACT trial demonstrated that once-daily single-inhaler triple therapy (SITT) significantly reduces exacerbations versus dual therapies. Blood eosinophils and smoking status may be important modifiers of treatment response to ICS. Modelling of these relationships and their interactions, including outcomes beyond exacerbations, was undertaken here.

Methods: IMPACT was a randomised, double-blind, parallel-group, 52-week, global study comparing once-daily SITT (fluticasone furoate/umeclidinium/vilanterol [FF/UMEC/VI]) with dual inhaled therapy (FF/VI and UMEC/VI). Eligible patients had moderate-to-very-severe COPD and ≥1 moderate/severe exacerbation in the previous year. Fractional polynomials were used to model continuous blood eosinophil counts. Negative binomial regression was used for numbers of moderate/severe exacerbations, severe exacerbations and pneumonia. Differences at Week 52 in trough forced expiratory volume in 1 second (FEV_1), St George's Respiratory Questionnaire (SGRQ) total score and Transition Dyspnoea Index (TDI) were modelled using repeated measurements mixed effect models.

Findings: The magnitude of benefit of ICS-containing arms (FF/UMEC/VI [N=4,151] and FF/VI [N=4,134]) versus a non-ICS dual long-acting bronchodilator (UMEC/VI [N=2,070]) in reducing moderate/severe exacerbation rates increased in proportion to blood eosinophil count. For example, the moderate/severe exacerbation rate ratio (95% confidence interval [CI]) for FF/UMEC/VI versus UMEC/VI was 0·88 (0·74, 1·04) at blood eosinophil count <90 cells/µL and 0·56 (0·47, 0·66) at ≥310 cells/µL; the corresponding rate ratio for FF/VI versus UMEC/VI was 1·09 (0·91, 1·29) and 0·56 (0·47, 0·66), respectively. Similar results were observed for FEV_1, TDI and SGRQ total score; however, the relationship with FEV_1 was less marked. At blood eosinophil counts <90 and ≥310 cells/µL, the FF/UMEC/VI versus UMEC/VI treatment difference (95% CI) was 40 mL (10, 70) and 60 mL (20, 100) for trough FEV_1, -0·01 (-0·68, 0·66) and 0·30 (-0·37, 0·97) for TDI score, and -0·01 (-1·81, 1·78) and -2·78 (-4·64, -0·92) for SGRQ total score, respectively. Smoking status modified the relationship between observed efficacy and blood eosinophil count for moderate/severe exacerbations, TDI and FEV_1, with former smokers more corticosteroid responsive at any eosinophil count than current smokers.

Interpretation: This analysis of the IMPACT trial demonstrates that assessment of blood eosinophil count and smoking status has the potential to optimise ICS use in clinical practice in patients with COPD and a history of exacerbations.

INTRODUCTION

The 2019 Global initiative for chronic Obstructive Lung Disease (GOLD) strategy document recommends that pharmacological therapy for chronic obstructive pulmonary disease (COPD) aims to reduce symptoms and the frequency and severity of exacerbations,[1] which are significant contributing factors to the high clinical and economic burden of the disease.[2-4]

Inhaled corticosteroids (ICS) reduce exacerbation rates in patients with COPD and a history of exacerbations.[5-8] However, the heterogeneity of COPD leads to variability between individuals in the magnitude of ICS benefit, and the potential for adverse side effects such as pneumonia.[9] Post hoc and pre-specified analyses of randomised controlled trials have shown that higher blood eosinophil counts are associated with greater ICS treatment effects.[10-13] A pooled analysis of clinical trials comparing ICS/long-acting β_2-agonist (LABA) combination therapy (N=4,528) with LABA monotherapy modelled this relationship; beneficial effects of ICS on exacerbation reduction were apparent at >100 eosinophils/µL, with greater effects observed at higher blood eosinophil levels.[14] Dichotomising the eosinophil count into high and low based on an arbitrary threshold[10,11] cannot fully describe the continuous nature of the relationship between blood eosinophils and ICS effect.[14] The increasing effect of ICS at higher blood eosinophil counts has also been observed in other analyses of ICS/LABA versus LABA clinical trials using multiple eosinophil subgroups.[11,12]

Recent clinical trials have demonstrated the benefits of single-inhaler triple therapy (SITT) versus the dual combination treatments ICS/LABA and long-acting muscarinic antagonist (LAMA)/LABA on exacerbation prevention.[15-18] Data modelling to understand the ability of blood eosinophils to better describe the effects of triple therapy versus LAMA/LABA, and ICS/LABA versus LAMA/LABA is needed to support the use of this biomarker to aid decision-making regarding the use of these combination treatments in clinical practice. The InforMing the PAthway of COPD Treatment (IMPACT) trial was designed to establish the relative benefits of the SITT containing fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI [ICS/LAMA/LABA]) compared with both FF/VI (ICS/LABA) and UMEC/VI (LAMA/LABA) in patients with moderate-to-very-severe COPD and at risk of exacerbation.[18,19] In IMPACT, 47% of patients had ≥2 moderate exacerbations and 26% had ≥1 severe exacerbation in the year prior to enrolment.[18] The IMPACT results have been reported elsewhere, and demonstrated that SITT reduced moderate/severe COPD exacerbations, improved lung function and improved quality of life (QoL) compared with either dual combination therapy.[18] There was also a reduction in the risk of on-treatment mortality with SITT versus UMEC/VI.[18] In a pre-specified analysis, a greater reduction in annual moderate/severe exacerbation rates was reported with SITT

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versus UMEC/VI in patients with ≥150 eosinophils/µL compared with those with <150 eosinophils/µL.

Recent studies comparing SITT with LAMA/LABA, and ICS/LABA with LAMA/LABA, have used different bronchodilator molecules within the dual bronchodilator compared with the ICS containing combination.[17,20] Furthermore, different inhaler devices and dosing regimens (once vs twice a day) have been compared which can introduce confounding. A strength of the IMPACT trial is the use of the same bronchodilator molecules, inhaler devices, doses, and dosing regimen for all treatments, meaning that any differences observed cannot be attributed to these variables.[18]

We report an analysis of the IMPACT trial that undertook modelling of the relationship of blood eosinophil counts with ICS therapy across multiple clinical outcomes including exacerbations, lung function and health status. The novelty of this analysis resides in that it is the first data modelling of triple therapy or ICS/LABA versus LAMA/LABA, and in the unique high exacerbation risk nature of the IMPACT population compared with other recent clinical trials comparing combination treatments.[15,20] A strength of this analysis is the large sample size. It has previously been reported that current smoking modifies the relationship between blood eosinophil counts and ICS effect, with a greater ICS effect observed in former smokers.[14,21,22] We therefore also evaluated the effect of current or former smoking on this relationship in post hoc analyses.

METHODS

Study design

Details of the IMPACT trial design (GSK study number CTT116855; NCT02164513) have been published previously.[18,19] Briefly, IMPACT was a Phase III, randomised, double-blind, parallel-group, multicentre study. Patients remained on their own medication during a 2-week run-in period and were then randomised 2:2:1 to once-daily SITT containing ICS/LAMA/LABA (FF/UMEC/VI 100/62·5/25 µg), once-daily dual therapy ICS/LABA (FF/VI 100/25 µg) or LAMA/LABA (UMEC/VI 62·5/25 µg), administered via the Ellipta inhaler. The primary objective of the IMPACT trial was to evaluate the effect of SITT on the annual rate of moderate/severe COPD exacerbations compared with both dual combinations over 52 weeks.[18] One of the secondary objectives was to compare the annual rate of on-treatment moderate/severe exacerbations between SITT and LAMA/LABA (UMEC/VI) by blood eosinophil counts <150 eosinophils/µL and ≥150 eosinophils/µL at baseline. In the analyses presented here, blood eosinophil count was modelled as a continuous measure in the overall population and by baseline smoking status to describe the effect of ICS on the rate of on-

treatment moderate/severe exacerbations in patients treated with SITT versus UMEC/VI. The rate of severe (hospitalised) exacerbations and exacerbations treated with oral corticosteroids (OCS) and/or antibiotics, trough forced expiratory volume in 1 second (FEV_1), St George's Respiratory Questionnaire (SGRQ) total score and Transition Dyspnoea Index (TDI) score at Week 52, and the rate of pneumonia were also examined.

Patients

Eligible patients were ≥40 years of age and symptomatic (COPD Assessment Test [CAT] score of 10 or more; range 0–40; higher scores indicate more symptoms) with a FEV_1 <50% of predicted normal and a history of at least one moderate or severe exacerbation in the previous year, or FEV_1 of 50–80% of predicted normal and at least two moderate or one severe exacerbation in the previous year. Full inclusion and exclusion criteria have been previously described.[18,19]

Assessments and variables

Demographics and baseline characteristics including baseline blood eosinophil count, smoking status, total CAT score (range 0–40; higher scores indicate more symptoms), GOLD grade, lung function test results, concomitant COPD medications and exacerbation history were assessed at screening. Exacerbations were assessed as moderate (requiring treatment with antibiotics and/or OCS) or severe (resulting in hospitalisation or death); spirometry was performed to assess trough FEV_1; symptom scores were measured by the TDI (range -9–9; lower values indicate worsening severity of dyspnoea), and health-related QoL (HRQoL) was measured by the SGRQ total score (range 0–100; lower scores indicate better HRQoL); results for these outcomes at Week 52 are presented here. Reversibility testing was performed as previously described.[19] Pneumonia and other adverse events (AEs) were captured as AEs of special interest (AESI) pre-defined as a group of Medical Dictionary for Regulatory Activities preferred terms.

Statistical methods

Analyses of annual rates of moderate/severe exacerbations, trough FEV_1 and SGRQ using baseline blood eosinophil count as a continuous variable were pre-specified. The comparison of FF/VI with UMEC/VI was not described in the IMPACT protocol but was added to the analysis plan and pre-specified prior to unblinding of the study. The form of the model used fractional polynomials to model the relationship between each endpoint and blood eosinophil count and to select the best model, allowing more flexibility in the form of the relationship. The IMPACT protocol included comparisons of SITT with LAMA/LABA for ≥150 eosinophils/μL for the following key endpoints: rate

of moderate/severe exacerbations; time to first moderate/severe exacerbation; rate of severe exacerbations. Analyses of each endpoint by <150 and ≥150 eosinophils/µL (including FEV_1 and CAT/SGRQ/TDI) were pre-specified. Prior to unblinding of the study, modelling of the relationship between continuous eosinophil counts and trough FEV_1, SGRQ and rate of moderate/severe exacerbations was added to the analysis plan; however, the use of fractional polynomials was not pre-specified. The relationship between outcomes and blood eosinophil count by smoking status was examined post hoc. Further analyses of exacerbation types (those treated with antibiotics only; with OCS only; with antibiotics with or without OCS; with OCS with or without antibiotics; and with both antibiotics and OCS), severe exacerbations, pneumonia and TDI were also conducted post hoc. Analyses of the number of exacerbations were performed using a negative binomial model retaining the covariates from primary pre-specified analysis models of this endpoint:[18] treatment group, sex, exacerbation history (≥1, ≥2 moderate/severe), smoking status, geographical region, and post-bronchodilator percent predicted FEV_1. Additionally, blood eosinophil count was transformed using two fractional polynomials terms which were both included in the model as continuous covariates. Treatment group by eosinophil covariates interactions were also included in the model allowing the magnitude of the interaction (but not the order of the fractional polynomial transformation) to differ with each treatment group. The best fitting model from the two-term fractional polynomial class of 36 pre-determined fractional polynomial models was selected based on likelihood.[23] Occasionally models had fitting issues (did not converge or did not converge satisfactorily) and these models were removed from consideration. The selected best fitting model was plotted as continuous eosinophil count versus exacerbation rate in each treatment arm. Further information regarding the criteria used for model selection is included in Supplementary File 1.

FEV_1, SGRQ and TDI were analysed using an analogous process for repeated measures mixed effect models with additional covariates of geographical region, visit, relevant baseline, baseline by visit, treatment group by visit. The number of pneumonia AESI was analysed using negative binomial regression models with geographical region as an additional covariate. Separate models using eosinophil quintile subgroups are described in Supplementary File 2.

The exacerbation models adjusted for potential confounding factors including sex, exacerbation history (≥1 or ≥2 moderate/severe), smoking status, geographical region and post-bronchodilator percent predicted FEV_1. The models for FEV_1, SGRQ and TDI adjusted for smoking status, geographical region and the relevant baseline.

Rate ratios (RR) and confidence intervals (CI) corresponding to the model for specific eosinophil values are also presented. The eosinophil levels chosen are arbitrary and act only as examples.

P-values have not been included as the aim of this analysis was to model the form of the relationship rather than to perform significance testing.

Data sharing

Anonymised individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com

Role of the funding source

This study was funded by GlaxoSmithKline (GSK). The funders of the study had a role in the study design, data analysis, data interpretation and writing of the report.

RESULTS

Detailed characteristics of the IMPACT trial population have been published previously, and no clinically relevant differences among the three treatment groups were identified.[18] Overall, 10,333 patients had available baseline blood eosinophil count data (FF/UMEC/VI [n=4,143]; FF/VI [n=4,125]; UMEC/VI [n=2,065]). The majority of patients were male (66% [6,856/10,333]), former smokers (65% [6,756/10,333]) with a mean smoking history of 46·6 pack years, and had a mean age of 65·3 years.[18] Forty-seven percent (4,872/10,333) had two or more moderate exacerbations in the previous year, the mean post-bronchodilator FEV_1 % predicted normal was 45·5%, and the mean total CAT score was 20·1.[18] At baseline (screening date), 71% (7,351/10,333) of patients were receiving ICS-containing therapy. The distribution of blood eosinophil counts at baseline is shown in Figure 1 and Supplementary Table S1, and was similar across the three treatment arms, with an overall median count of 170 eosinophils/µL (Table 1). The relationship between baseline blood eosinophil count and FEV_1 reversibility were specifically studied at screening (Supplementary Figure S1) and no relationship was demonstrated.

As previously reported, the adjusted mean annual rate of exacerbations (adjusted for sex, exacerbation history [≤1, ≥2 moderate/severe], smoking status, geographical region and post-bronchodilator percent predicted FEV_1) was 0·91, 1·07 and 1·21 in the FF/UMEC/VI, FF/VI, and UMEC/VI treatment groups, respectively.[18] Exacerbation rates in the non-ICS treatment arm (UMEC/VI) increased with increasing blood eosinophil counts. In contrast, the rate of moderate/severe exacerbations in ICS-containing treatment arms (FF/UMEC/VI and FF/VI) showed little change with increasing blood eosinophil count (Figure 2A, Supplementary Figure S2A and Supplementary Table S2 for quintile data). At blood eosinophil counts <90 and ≥310 cells/µL,

moderate/severe exacerbation rates (95% CI) were 0·83 (0·75, 0·91) and 1·03 (0·93, 1·13) for FF/UMEC/VI, 1·02 (0·93, 1·13) and 1·02 (0·93, 1·13) for FF/VI, and 0·94 (0·82, 1·09) and 1·83 (1·61, 2·09) for UMEC/VI, respectively (Supplementary Table S2). The effect of FF/UMEC/VI on reducing the rate of moderate/severe exacerbations was greater compared with UMEC/VI at greater than approximately 100 eosinophils/μL (RR [95% CI] at 100 eosinophils/μL: 0.88 [0.80, 0.97]). Exacerbation rates were lower with UMEC/VI versus FF/VI at lower blood eosinophil counts (RR [95% CI] at 100 eosinophils/μL: 0.92 [0.84, 1.01]), but as counts increased (above approximately 200 eosinophils/μL) the exacerbation rate with UMEC/VI was greater compared with FF/VI (RR [95% CI] at 200 eosinophils/μL: 1.10 [1.01, 1.18]). As baseline blood eosinophil count increased, the treatment difference between FF/UMEC/VI versus UMEC/VI and FF/VI versus UMEC/VI for moderate/severe exacerbations increased (Figure 2B, Supplementary Figure S2B and Supplementary Table S3). The interaction between treatment groups and baseline eosinophil count was significant (p<0·0001), as was the interaction for each pair of treatments: FF/UMEC/VI versus UMEC/VI (p<0·0001) and between FF/VI versus UMEC/VI (p<0·0001). Treatment differences for the rate of severe exacerbations (i.e. exacerbations requiring hospitalisation) showed a similar pattern (Figure 2C, Supplementary Figure S2C and Supplementary Table S4).

The beneficial effect on reducing moderate/severe exacerbations observed with ICS-containing treatment was more pronounced in former smokers (RR [95% CI] FF/UMEC/VI vs UMEC/VI: 0·70 [0·64, 0·77] and FF/VI vs UMEC/VI: 0·83 [0·75, 0·91]) than current smokers (0·86 [0·76, 0·98] and 1·01 [0·89, 1·15], respectively). The difference in the treatment effect (FF/UMEC/VI vs UMEC/VI) between the former smokers and current smokers was significant (p=0·011) as was the difference between FF/VI versus UMEC/VI (p=0·014).

The magnitude of the ICS benefit increased with higher blood eosinophil counts in both current and former smokers, but there was a lower treatment effect in current smokers at all blood eosinophil levels (Figures 3, Supplementary Figure S3 and S4 and Supplementary Table S5). In former smokers, ICS benefits were observed at all blood eosinophil levels when comparing FF/UMEC/VI with UMEC/VI, whereas in current smokers no ICS benefit was observed at lower eosinophil counts, below approximately 200 eosinophils/μL (Figures 3 and Supplementary Figure S4). A similar pattern was observed in the rates of severe exacerbations (Figures 4, Supplementary Figure S5 and Supplementary Table S6). The effect of smoking by pack years was also analysed; however, it did not influence the relationship between treatment effect and eosinophils (data not shown).

The comparison of ICS-containing treatments versus UMEC/VI showed increasing effect sizes at higher baseline blood eosinophil counts for TDI and SGRQ total score at Week 52. The relationship with FEV_1 was suggestive of a similar effect but not as clear as for the other endpoints (Figures 5, Supplementary Figure S6 and Supplementary Tables S7–S9). The interaction between treatment groups and baseline eosinophil count was significant for TDI (p=0·013), SGRQ total score (p=0.0045) and FEV_1 (p=0·019). At all baseline blood eosinophil counts, the improvement in FEV_1 was greater with UMEC/VI versus FF/VI. The interaction between treatment and smoking status was significant for TDI (p=0.025) and FEV_1 (p=0.028) but not for SGRQ (p=0.16). Consistent with exacerbation results, the magnitude of ICS benefit on TDI, SGRQ total score and FEV_1 increased with higher blood eosinophil counts in both current and former smokers (Supplementary Figures S7–S9 and Tables S10–S12). For example, the FF/UMEC/VI versus UMEC/VI treatment difference (95% CI) in SGRQ total score at Week 52 at blood eosinophil counts <90 and ≥310 cells/μL was 1·18 (-1·75, 4·11) and -1·84 (-4·94, 1·25) in current smokers, and -0·85 (-3·12, 1·42) and -3·01 (-5·34, -0·69) in former smokers, respectively (Supplementary Figure S7 and Table S10).

Consistent with the analyses above, the rate of moderate/severe exacerbations requiring OCS or both OCS and antibiotics decreased for both FF/UMEC/VI versus UMEC/VI and FF/VI versus UMEC/VI as baseline eosinophil counts increased. The beneficial effect of ICS on moderate/severe exacerbations was greater at higher blood eosinophil counts for those exacerbations requiring OCS or antibiotics and OCS; there was no clear relationship with blood eosinophil counts for those requiring only antibiotics (Figure 6, Supplementary Figure S10 and Supplementary Tables S13 and S14).

No significant impact of blood eosinophil count on the rate of pneumonia was observed in the ICS-containing treatment arms. Rates of pneumonia AESI across all treatment arms have been previously described.[18] Pneumonia rates increased with UMEC-containing therapy in patients with higher versus lower blood eosinophil counts (approximately > or <450 eosinophils/μL, respectively); however, 95% CIs were wide (Supplementary Figure S11 and Supplementary Table S15). At blood eosinophil counts 300 and 600 cells/μL, annual pneumonia rates (95% CI) were 0·09 (0·08, 0·10) and 0·10 (0·08, 0·13) for FF/UMEC/VI, and 0·06 (0·05, 0·08) and 0·08 (0·05, 0·13) for UMEC/VI, respectively. The p-value for the interaction between treatment groups and baseline eosinophil count was p=0·44.

DISCUSSION

The IMPACT trial is the largest completed clinical trial comparing the effects of SITT (FF/UMEC/VI) to dual inhaled therapies (FF/VI and UMEC/VI) in symptomatic patients with COPD and a history of exacerbations.[18] Statistical modelling showed that the effects of FF/UMEC/VI compared with UMEC/VI on exacerbation reduction were dependent on blood eosinophil counts. In this analysis, there was no difference between FF/UMEC/VI compared with UMEC/VI at below approximately 100 eosinophils/µL; however, increasing blood eosinophil counts above this threshold were associated with progressively greater treatment differences in favour of FF/UMEC/VI. Comparisons between dual combination treatments also showed that the treatment differences were dependent on blood eosinophil counts, with lower counts favouring UMEC/VI and higher counts favouring FF/VI.

The rate of exacerbations in patients not treated with ICS increased at higher blood eosinophil counts. This shows for the first time that the addition of a LAMA does not alter the relationship between ICS efficacy and blood eosinophil counts, which has been seen in previous analyses of ICS/LABA versus LABA clinical trials.[11,12,14] The treatment difference between FF/UMEC/VI versus UMEC/VI therefore varied at different blood eosinophil counts, with no difference at the lowest counts and a continuous relationship showing greater effects at higher blood eosinophil counts. These results highlight that a single blood eosinophil threshold to subdivide patients simply into ICS "responders" and "non-responders" is an over simplification of the relationship between these variables, as the magnitude of the response varies above any "no-effect" threshold identified. In the whole IMPACT population, <100 eosinophils/µL was the estimated threshold that suggested no ICS effect when comparing FF/UMEC/VI versus UMEC/VI, which is the same value reported for a large pooled analysis of ICS/LABA versus LABA clinical trials.[14]

Previous clinical trials of triple therapy versus LAMA/LABA, including the IMPACT, TRIBUTE and KRONOS studies, demonstrated differential ICS effects on exacerbation prevention above and below an a priori defined single blood eosinophil threshold.[15,17,18] The KRONOS study also provided evidence of differential treatment effects on exacerbation rate reduction across an eosinophil count continuum in a low exacerbation risk population (N=1,902).[15] It is important to note that the determination of a cut-point may vary across studies due to differing sample sizes and population characteristics; studies with smaller sample sizes and/or fewer events will have less precision. The large sample size of the IMPACT trial (N=10,355) provides unique information in a high exacerbation risk population. The data modelling approach here did not define any threshold a priori but allowed the complexity of the relationship between ICS effects and blood eosinophil counts to be fully explored in this patient population at high risk of exacerbations. Our results provide support for the

recent recommendations in the GOLD 2019 report, where it is stated that thresholds of both 100 and 300 eosinophils/μL can be used in clinical practice as these provide different information i.e. <100 eosinophils/μL and >300 eosinophils/μL identifies individuals with the lowest and highest likelihood of a beneficial response to ICS treatment, respectively.[1]

We observed that the addition of FF to UMEC/VI resulted in a greater benefit for former smokers at all baseline eosinophil counts, while for current smokers a treatment difference was observed above approximately 200 eosinophils/μL. In former smokers, even those in the lowest quintile had a 16% reduction in exacerbation rates, and a treatment benefit was demonstrated at all baseline eosinophil counts. A similar "right shift in the dose (blood eosinophil count)-ICS response" curve was also reported in the data modelling of ICS/LABA versus LABA with regard to current smoking status.[14] These observations regarding differences according to smoking status are interesting when considering the large body of data showing that smoking confers relative corticosteroid resistance in both COPD and asthma.[24-29] Alternatively, active smoking is known to be immunosuppressive,[30] which could in turn potentially suppress the corticosteroid responsive elements of the inflammation mediating COPD. Overall, these results demonstrate the potential of blood eosinophil counts in conjunction with smoking status to predict the magnitude of ICS response within a dual or triple combination therapy. Future approaches to COPD pharmacological management should move beyond the simple dichotomisation of each clinical or biomarker variable, towards more complex algorithms that integrate the interactions between important variables including exacerbation history, smoking status and blood eosinophil counts. While randomisation of the treatment groups was not stratified by baseline eosinophil count or smoking status, the groups were balanced at baseline with respect to these factors.

The additional analyses on other outcome measures, such as TDI, SGRQ and FEV_1 demonstrated a relationship between ICS (FF) effects with triple therapy and blood eosinophil counts, which was perhaps clearest for SGRQ. These data support the exacerbation analysis, and the concept that blood eosinophil counts could globally predict the clinical benefits of ICS treatment in patients with COPD. Previous similar analyses have provided mixed results, which are likely related to limited sample sizes.[10,11,31] However, positive results for SGRQ and FEV_1 were reported in the large pooled analysis of budesonide/formoterol versus formoterol clinical trials.[14] While the main aim of the IMPACT trial was to investigate triple versus dual therapies, this analysis also compared the dual therapies FF/VI and UMEC/VI. As VI was the LABA in both combinations, this allowed the first direct comparison of adding a LAMA versus adding an ICS. In the overall population, the exacerbation rate

was lower with FF/VI versus UMEC/VI; we now show that the treatment advantage in the overall population with FF/VI was apparent only above approximately 200 eosinophils/µL. In addition, the comparative benefits on SGRQ and TDI indicated that at lower eosinophils levels UMEC produced numerically greater positive changes than FF, but at higher eosinophil levels FF numerically out-performed UMEC. Clinical decision making regarding the use of dual combination therapies can incorporate this information in a clinical assessment that predicts potential benefit alongside the risk of ICS adverse effects.[1]

Our results differ from the FLAME study, where the effects of ICS/LABA were not greater than LAMA/LABA at any blood eosinophil count.[20] There are many differences between the populations and design of the FLAME and IMPACT studies that may explain these differences: (1) IMPACT had a greater proportion of patients with two or more moderate or severe exacerbations in the previous year (19·3% in FLAME vs 54·6% in IMPACT); (2) In FLAME, 45% of patients were reversible (mean reversibility 22%) compared with 18% in IMPACT (mean reversibility 10·4%); (3) FLAME excluded patients with blood eosinophil count >600 eosinophils/µL; (4) FLAME required a run-in for a month on tiotropium which meant that subjects who potentially benefit from ICS therapy may have been excluded from randomisation.[18,20] The exacerbation history and hospitalisations are perhaps the most crucial differences, as FF/VI was similar to UMEC/VI at <200 eosinophils/µL but superior at >200 eosinophils/µL for severe exacerbations, suggesting that the ICS benefit becomes more pronounced in populations at very high risk of severe exacerbations. Nevertheless, also in FLAME, treatment differences showed clear gradation by eosinophil level.

There was no evidence of any relationship between blood eosinophil count and the rate of pneumonia nor with the rate of the excess of pneumonias seen in the FF treatment arms. Analysis of exacerbation events according to use of antibiotics or OCS showed a greater effect of ICS at higher blood eosinophil counts for preventing exacerbations requiring OCS; however, there was a pronounced overlap in treatment of exacerbations with both antibiotics and OCS. This potentially supports the concept that ICS treatment in patients with higher blood eosinophil counts has a more pronounced effect on exacerbation events not associated with bacterial infections.[32] Conversely, both ICS-containing arms versus the LAMA/LABA arm showed higher rates of events treated with antibiotics alone. The reasons for this are unclear, but the relationship appeared to be constant over the majority of the observed distribution of blood eosinophils, which is similar to that seen with excess pneumonia associated with ICS use and discordant with the benefits of ICS. These adverse

effects may relate to an immunomodulatory quality of ICS therapy that is mechanistically dissociated from the beneficial effects.

A limitation of this analysis is that the patients' history of prior asthma was not quantified, as this was not an exclusion criterion for the study. Furthermore, the study was aimed at patients with COPD as defined by American Thoracic Society/European Respiratory Society and GOLD criteria and patients with a current diagnosis of asthma were excluded,[1,33] and a previous valid diagnosis of asthma does not preclude the subsequent development of COPD in smokers. The investigators also excluded any patients whose symptoms were not felt to be due to COPD. The IMPACT population all met current criteria for COPD, all were heavy smokers and had lower reversibility compared with previous COPD studies where a prior diagnosis of asthma was an exclusion.

There is increasing emphasis on a precision medicine approach in COPD regarding the use of ICS, in order to optimise the benefit versus risk ratio at the individual patient level.[1,34,35] Precision medicine combines different clinical (phenotypic) factors with biological (endotypic) information, including biomarker results, to make optimal treatment decisions.[9] This analysis of the IMPACT trial in COPD patients with a history of at least one exacerbation in the year prior (clinical phenotype) demonstrates that blood eosinophil counts (biomarker for the eosinophilic COPD endotype) can predict ICS effects. There was also an effect of current smoking, as former smokers were more sensitive to the beneficial effects of ICS. Our results support a precision medicine approach using current smoking status and blood eosinophil counts in patients at increased risk of exacerbations to optimise the use of ICS in patients with COPD in clinical practice.

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Declaration of interests

Contributions

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors, take responsibility for the integrity of the work as a whole, contributed to the writing and reviewing of the manuscript, and have given final approval for the version to be published. All authors had full access to the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

S Pascoe, DA Lipson, C Compton, and N Barnes were involved in the conception/design of the study and analysis/interpretation of data. D Singh, A Papi, N Roche, G Brusselle, MK Han, S Lettis, B Hartley, RJP van der Valk, DA Lomas, R Wise, P Lange, and FJ Martinez were involved in analysis/interpretation of data. DMG Halpin, MT Dransfield and GJ Criner were involved in acquisition and analysis/interpretation of data.

TABLES AND FIGURES

Table 1. Baseline characteristics of patients with available baseline blood eosinophil count data

Characteristic	FF/UMEC/VI (N=4,143)	UMEC/VI (N=2,065)	FF/VI (N=4,125)	Total (N=10,333)
Age, years, mean ± SD	65·3 ± 8·3	65·2 ± 8·3	65·3 ± 8·3	65·3 ± 8·3
Female sex, n (%)	1,380 (33)	712 (34)	1,385 (34)	3,477 (34)
Post-bronchodilator FEV_1 % predicted normal, mean ± SD*	45·7 ± 15·0	45·4 ± 14·7	45·5 ± 14·8	45·5 ± 14·8
Total CAT score, mean ± SD[†]	20·1 ± 6·1	20·2 ± 6·2	20·1 ± 6·1	20·1 ± 6·1
GOLD grade (1–4), n (%)*				
Grade 1 (mild)	10 (<1)	4 (<1)	8 (<1)	22 (<1)
Grade 2 (moderate)	1,533 (37)	727 (35)	1,452 (35)	3,712 (36)
Grade 3 (severe)	1,929 (47)	1,014 (49)	2,026 (49)	4,969 (48)
Grade 4 (very severe)	665 (16)	319 (15)	638 (15)	1,622 (16)
Smoking status, n (%)				
Current smoker	1,430 (35)	726 (35)	1,421 (34)	3,577 (35)
Former smoker[‡]	2,713 (65)	1,339 (65)	2,704 (66)	6,756 (65)
Moderate/severe exacerbations in previous year, n (%)[§]				
0	2 (<1)	2 (<1)	5 (<1)	9 (<1)
1	1,848 (45)	929 (45)	1,901 (46)	4,678 (45)
2	1,826 (44)	887 (43)	1,766 (43)	4,479 (43)
≥3	467 (11)	247 (12)	453 (11)	1,167 (11)
≥2 moderate/severe exacerbations in previous year, n (%)[§]	2,293 (55)	1,134 (55)	2,219 (54)	5,646 (55)
COPD medication at screening, n (%)				
ICS+LABA+LAMA	1,579 (38)	826 (40)	1,560 (38)	3,965 (38)
ICS+LABA without LAMA	1,217 (29)	576 (28)	1,177 (29)	2,970 (29)
LAMA+LABA without ICS	360 (9)	184 (9)	330 (8)	874 (8)
ICS+LAMA without LABA	45 (1)	19 (<1)	41 (<1)	105 (1)
LAMA without LABA or ICS	288 (7)	146 (7)	346 (8)	780 (8)
ICS without LABA or LAMA	125 (3)	60 (3)	126 (3)	311 (3)
LABA without ICS or LAMA	109 (3)	48 (2)	111 (3)	268 (3)
No ICS, LABA or LAMA	420 (10)	206 (10)	434 (11)	1,060 (10)
ICS at screening, n (%)				

Yes	2,966 (72)	1,481 (72)	2,904 (70)	7,351 (71)
No	1,177 (28)	584 (28)	1,221 (30)	2,982 (29)
Reversibility to Salbutamol[‖]				
n (%)	733 (18)	366 (18)	807 (20)	1,906 (18)
mean (SD), mL	105.8 (129.3)	101.0 (125.3)	109.2 (132.0)	106.2 (129.6)
Baseline blood eosinophil count (eosinophils/µL), median (IQR)	160 (90–270)	170 (100–280)	170 (100–270)	170 (90–270)

Patients received a once-daily inhaled combination of 100 µg FF, 62·5 µg UMEC and 25 µg VI in the FF/UMEC/VI group; 62·5 µg UMEC and 25 µg VI in the UMEC/VI group; and 100 µg FF and 25 µg VI in the FF/VI group.

*FF/UMEC/VI: n=4,137; UMEC/VI: n=2,064; FF/VI: n=4,124; total: n=10,325.

[†]FF/UMEC/VI: n=4,134; UMEC/VI: n=2,056; FF/VI: n=4,115; total: n=10,305.

[‡]Former smokers were defined as those who had stopped smoking at least 6 months prior to screening.

[§]Moderate exacerbation defined as leading to treatment with antibiotics or systemic glucocorticoids; severe exacerbation defined as resulting in hospitalisation or death.

[‖]Reversible is an increase in FEV_1 of ≥12% and ≥200 mL following administration of salbutamol. Not reversible is an increase in FEV_1 of <200 mL or a ≥200 mL increase that is <12% of the pre-salbutamol FEV_1. FF/UMEC/VI: n=4,136; UMEC/VI: n=2,063; FF/VI: n=4,124; total: n=10,323.

CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; GOLD, Global initiative for chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; SD, standard deviation; UMEC, umeclidinium; VI, vilanterol.

Figure Legends

Figure 1. Distribution of blood eosinophil counts at baseline

Figure 2. Annual rates of moderate/severe exacerbations by baseline blood eosinophil count and individual treatment arm (A), and between-treatment ratios for rates of moderate/severe exacerbations (B) and severe exacerbations (C)

CI, confidence interval; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol.

Figure 3. Between treatment differences (FF/UMEC/VI vs UMEC/VI) in the total study population in rates of moderate/severe exacerbations by baseline blood eosinophil count and smoking status

CI, confidence interval; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol.

Figure 4. Between treatment differences (FF/UMEC/VI vs UMEC/VI) in rates of severe exacerbations by baseline blood eosinophil count and smoking status

CI, confidence interval; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol.

Figure 5. Between-treatment differences in SGRQ total score (A), trough FEV$_1$ (B) and TDI score (C) at Week 52 by baseline blood eosinophil count

CI, confidence interval; FEV1, forced expiratory volume in 1 second; FF, fluticasone furoate; SGRQ, St George's Respiratory Questionnaire; TDI, Transition Dyspnoea Index; UMEC, umeclidinium; VI, vilanterol.

Figure 6. Between-treatment differences in moderate/severe exacerbations requiring only antibiotics (A), only OCS (B), or both antibiotics and OCS (C) by baseline blood eosinophil count

CI, confidence interval; FF, fluticasone furoate; OCS, oral corticosteroids; UMEC, umeclidinium; VI, vilanterol.

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