# A single blood eosinophil count measurement is as good as two for prediction of ICS treatment response in the IMPACT trial



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*To the Editor:*

Blood eosinophil count is a readily available biomarker in COPD that can assist identification of patients most likely to benefit from inhaled corticosteroids (ICS) [1]. Recent evidence has demonstrated a link between blood eosinophil count as a continuous variable and magnitude of response to ICS in terms of exacerbation rate reduction [2, 3]. The current Global Initiative for Chronic Obstructive Lung Disease (GOLD) report recommends that blood eosinophil count can be used to predict the likelihood of beneficial response to ICS, in combination with clinical assessment of exacerbation risk [1]. However, as blood eosinophil counts can show variability, particularly at higher levels [4–6], it is of clinical interest to determine how many measurements are sufficient to predict an ICS response in patients with COPD. Data from the InforMing the PAthway of COPD Treatment (IMPACT) trial showed an association between blood eosinophil count and ICS response on reduction of moderate/severe COPD exacerbations [3]. This *post hoc* analysis of IMPACT compared whether one or two measurements of blood eosinophil count can better predict ICS responses in patients with COPD.

Details of the design of IMPACT have been published previously (GSK study number CTT116855; ClinicalTrials.gov identifier NCT02164513) [7, 8]. Briefly, IMPACT was a 52-week, randomised, double-blind, parallel-group, multicentre study in patients ⩾40 years of age with symptomatic COPD (COPD Assessment Test score of ⩾10), and either forced expiratory volume in 1 s ($FEV_1$) <50% of predicted and a history of ⩾1 moderate or severe exacerbation in the previous year, or $FEV_1$ of 50 to <80% predicted and ⩾2 moderate or ⩾1 severe exacerbation in the previous year. Patients remained on their own medication during a 2-week run-in period and were then randomised (2:2:1) to receive once-daily single-inhaler triple therapy with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) 100/62.5/25 µg (ICS/long-acting muscarinic antagonist (LAMA)/long-acting $\beta_2$-agonist (LABA)), dual ICS/LABA therapy with FF/VI 100/25 µg, or dual LAMA/LABA therapy with UMEC/VI 62.5/25 µg. Blood eosinophil counts were measured at screening (2 weeks prior to day 1) and at randomisation (day 1) [3, 7, 8]. Patients who exacerbated during the run-in prior to randomisation and required steroids were excluded from the study and were not included in this analysis.

This *post hoc* analysis modelled the treatment effect of FF/UMEC/VI *versus* UMEC/VI, and FF/VI *versus* UMEC/VI on moderate/severe exacerbation rates by continuous blood eosinophil count using measurements taken at screening, randomisation, and the mean, minimum and maximum of the screening and randomisation blood eosinophil count values. For each of the five blood eosinophil count metrics, 36 different negative binomial models were fitted in order to identify the best-fitting model. Each model included the following covariates: treatment group, sex, exacerbation history (⩽1, ⩾2 moderate/severe), smoking status (screening), geographical region, post-bronchodilator % predicted $FEV_1$ (screening), transformed eosinophils, and transformed eosinophils by treatment. The treatment effect at different eosinophils levels was estimated for each model. The best-fitting model for each of the five blood eosinophil count metrics was selected using the Akaike information criterion (AIC), which estimates the amount of information lost by a model, such that the lowest AIC value indicates the best-fitting model. The models with the lowest AIC value for each of the five blood eosinophil count metrics are reported.

Shareable abstract (@ERSpublications)
**This *post hoc* analysis of the IMPACT trial demonstrated that a single blood eosinophil count measurement is sufficient to predict a beneficial response to inhaled corticosteroids in patients with symptomatic COPD and a history of exacerbations** https://bit.ly/3wgeDCU

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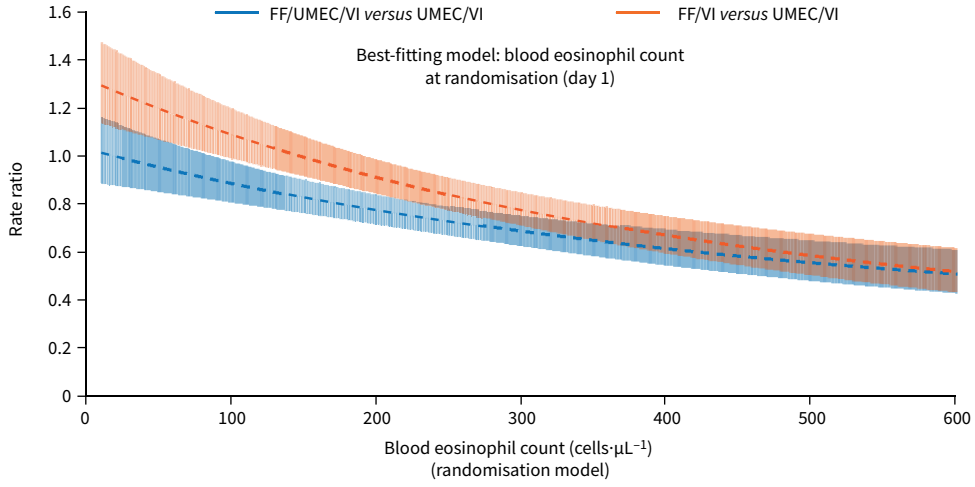
Baseline characteristics of the IMPACT study population have been reported previously, and there were no clinically relevant differences between the three treatment groups [7]. Blood eosinophil count data were available at screening for 10 333 patients (FF/UMEC/VI, n=4143; FF/VI, n=4125; UMEC/VI, n=2065) [3]. The mean and median eosinophil count was 210 cells·μL$^{-1}$ and 160 cells·μL$^{-1}$ at screening and 220 cells·μL$^{-1}$ and 170 cells·μL$^{-1}$ at randomisation (day 1) respectively, giving a median (interquartile range) difference of 10 (−40, 60) cells·μL$^{-1}$ between the average measurements. The best-fitting negative binomial models for each blood eosinophil count metric showed comparable AIC values, with the blood eosinophil count metric measured at study randomisation the best-fitting model (figure 1) and blood eosinophil count measured at screening the least well-fitting model. However, any blood eosinophil count measurement substantially improved the model compared with no measurement ($p<0.001$). All five metrics gave similar predictions for response to ICS treatment suggesting that any of the metrics are suitable in predicting ICS treatment response, and each metric made essentially identical predictions of the benefit of therapy, as can be seen for the FF/UMEC/VI *versus* UMEC/VI predictions reported in figure 1.

To our knowledge, this is the first analysis to demonstrate that one blood eosinophil count is sufficient for prediction of ICS treatment response. All five models gave similar predictions, confirming that any variation in blood eosinophil count over a 2-week period has no clinically relevant impact. These data should reassure clinicians that the timing of blood eosinophil count measurement is not critical for accurate prediction of ICS response in a population of patients with COPD, at least over a short time period. Of the five metrics, we found the best-fitting metric to be the one using actual data from day 1 at randomisation (figure 1); this metric was used in previous analyses of the effect of blood eosinophil count and smoking




| Rate Ratio FF/UMEC/VI *versus* UMEC/VI | | | | | |
|---|---|---|---|---|---|
| Screening model (AIC: 25389.5) | 0.88 (0.80, 0.97) | 0.76 (0.70, 0.82) | 0.68 (0.61, 0.75) | 0.62 (0.55, 0.70) | 0.58 (0.50, 0.66) |
| Randomisation model (AIC: 25365.8) | 0.89 (0.81, 0.98) | 0.78 (0.72, 0.84) | 0.69 (0.63, 0.75) | 0.61 (0.54, 0.69) | 0.56 (0.48, 0.65) |
| Mean model (AIC: 25375.1) | 0.89 (0.81, 0.99) | 0.76 (0.70, 0.82) | 0.67 (0.61, 0.74) | 0.62 (0.55, 0.69) | 0.57 (0.50, 0.66) |
| Minimum model (AIC: 25383.5) | 0.85 (0.78, 0.93) | 0.74 (0.68, 0.80) | 0.65 (0.58, 0.72) | 0.57 (0.49, 0.67) | 0.51 (0.43, 0.62) |
| Maximum model (AIC: 25376.2) | 0.91 (0.82, 1.01) | 0.79 (0.73, 0.86) | 0.71 (0.65, 0.77) | 0.65 (0.58, 0.72) | 0.60 (0.53, 0.69) |

**FIGURE 1** Modelled effect of FF/UMEC/VI *versus* UMEC/VI and FF/VI *versus* UMEC/VI treatment on moderate/severe exacerbation rate, according to the best-fitting model. Note: The table shows the exacerbation rate ratio for FF/UMEC/VI *versus* UMEC/VI for each of the five models that were applied. The overall best-fitting model highlighted uses eosinophils measured at randomisation. AIC: Akaike information criterion; FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol.

status on modification of ICS treatment response [3]. Furthermore, this analysis showed that use of two blood eosinophil count values did not provide additional information to predict an ICS response in this population, compared with using only one value, although it should be acknowledged that this current analysis does not explore the value of one eosinophil count over multiple eosinophil counts. It is important to note that data on blood eosinophil count and ICS response used for modelling in this analysis were based on confirmed, stable state values, in view of the fact that acute illness (particularly sepsis), oral prednisolone therapy and other factors may suppress blood eosinophil count [9, 10].

Potential limitations of this analysis include the 2-week time difference between the randomisation model and screening measurements, which some may consider to be a short timeframe between blood eosinophil count assessments, and the low number of blood eosinophil counts assessed per patient. In clinical practice, there are often larger gaps between measurements and we cannot determine from this study whether multiple measurements over a longer period of time would be more reliable. The use of patients from a clinical trial also restricted the analysis to those with relative clinical stability who had been exacerbation-free for a defined period prior to eosinophil measurements. As such, the population may not be truly representative of a real-world COPD population. Furthermore, prior treatment was not included as a covariate in the modelling analysis. Nonetheless, the analysis was conducted in a large population (>10 000 patients), allowing assessment of the utility of eosinophil measurements at a population level; studies with smaller sample sizes or fewer events are likely to be less precise than those with larger populations, such as IMPACT [3]. As such, these data provide valuable and robust information on the acceptability of one blood eosinophil count measurement in the prediction of response to ICS treatment.

In conclusion, through modelling of data from patients with symptomatic COPD and a history of exacerbations in the IMPACT trial, no improvement was demonstrated in prognostic value of a repetition of blood eosinophil count over a short period of time (2 weeks) compared with a single measurement. This analysis indicates that a single blood eosinophil count measurement, taken in steady state, could potentially be used to predict a beneficial response to ICS, supporting the recommendations of the GOLD 2020 report [1].

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