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

Mona Bafadhel,[1] Neil Barnes,[2,3] Stephen C. Bourke,[4] Chris Compton,[2] Gerard J. Criner,[5] Mark T. Dransfield,[6] David M.G. Halpin,[7] MeiLan K. Han,[8] Benjamin Hartley,[9] C. Elaine Jones,[10] Peter Lange,[11,12] Sally Lettis,[13] David A. Lipson,[14,15] David A. Lomas,[16] Neil Martin,[2,17] Fernando J. Martinez,[18] Robert Wise,[19] Dave Singh[20]

[1]Nuffield Department of Medicine, University of Oxford, Oxford, UK; [2]GSK, Brentford, Middlesex, UK; [3]Barts and the London School of Medicine and Dentistry, London, UK; [4]North Tyneside General Hospital, North Shields, and Newcastle University, Newcastle, UK; [5]Lewis Katz School of Medicine at Temple University, Philadelphia, PA, USA; [6]Division of Pulmonary, Allergy, and Critical Care Medicine, Lung Health Center, University of Alabama at Birmingham, Birmingham, AL, USA; [7]University of Exeter Medical School, College of Medicine and Health, University of Exeter, Exeter, Devon, UK; [8]University of Michigan, Pulmonary & Critical Care, Ann Arbor, MI, USA; [9]Veramed Ltd, Twickenham, UK; [10]GSK, Research Triangle Park, NC, USA; [11]Department of Public Health, University of Copenhagen, Copenhagen, Denmark; [12]Herlev-Gentofte Hospital, Herlev, Denmark; [13]GSK, Stockley Park West, Uxbridge, Middlesex, UK; [14]GSK, Collegeville, PA, USA; [15]Pulmonary, Allergy, and Critical Care Division, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [16]UCL Respiratory, University College London, London, UK; [17]University of Leicester, Leicester, UK; [18]New York-Presbyterian Hospital/Weill Cornell Medical Center, New York, NY, USA; [19]Division of Pulmonary and Critical Care Medicine, Johns Hopkins Medicine, Baltimore, MD, USA; [20]University of Manchester, Manchester, UK

Current manuscript counts

Body text: 1218/1500 permitted

References: 10 of 15 permitted

Figure/Table: 1 of 1 permitted

To the Editor:

Blood eosinophil count is a readily available biomarker in chronic obstructive pulmonary disease (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 second (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 β_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.

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 and 160 cells/µL at screening and 220 cells/µL and 170 cells/µL at randomisation (Day 1) respectively, giving a median

(interquartile range) difference of 10 (-40, 60) cells/µL 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**) 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 FF/UMEC/VI versus UMEC/VI predictions reported in the **Figure**.

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**); this metric was used in previous analyses of the effect of blood eosinophil count and smoking 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]

Availability of data and material

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

Acknowledgements

This study was funded by GlaxoSmithKline (GSK; CTT116855; Clinicaltrials.gov identifier: NCT02164513). Editorial support (in the form of writing assistance, assembling figures, collating author comments, grammatical editing and referencing) was provided by Eloise Morecroft and Katie Baker, at Fishawack Indicia Ltd, UK, and was funded by GSK. Dave Singh is supported by the National Institute for Health Research (NIHR) Manchester Biomedical Research Centre (BRC). David Lomas is is supported by the National Institute for Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre (BRC). He is an NIHR Senior Investigator.

Author contributions

M. Bafadhel, N. Barnes, S.C. Bourke, C. Compton, B. Hartley, S. Lettis, D.A. Lipson, N. Martin and D. Singh contributed to the conception/design of this analysis. G.J. Criner, M.T. Dransfield and D.M.G. Halpin were also involved in acquisition of data, and all authors were involved in analysis and interpretation of the data and editing of the article and approved the final version of the manuscript before submission.

Disclosures

M. Bafadhel reports grants from AstraZeneca; advisory board attendance for AstraZeneca, Chiesi, Boehringer Ingelheim and GSK (in the last 3 years); attendance at educational meetings facilitated by

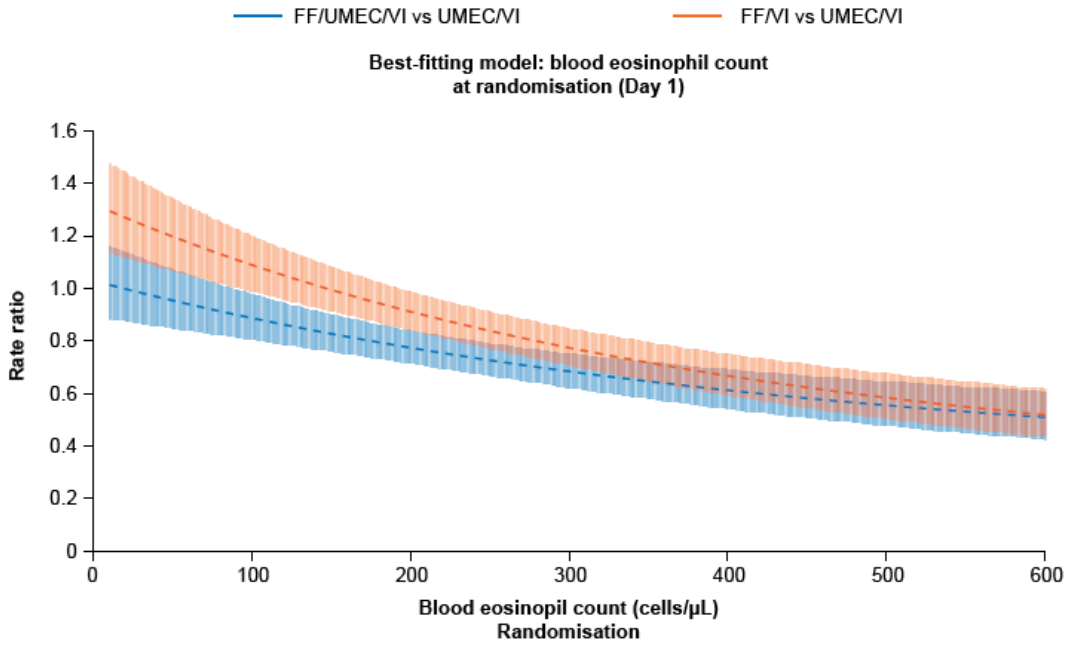
AstraZeneca, Chiesi and Boehringer Ingelheim (in the last 3 years); and scientific advisor for ProAxsis and AlbusHealth. N. Barnes, C. Compton, C.E Jones, S. Lettis, D.A. Lipson and N. Martin are employees of GSK and hold stocks and shares in GSK. S.C. Bourke reports research grants from GSK, Philips, ResMed and Pfizer Open Air, support to attend scientific meetings from Boehringer Ingelheim, Chiesi, GSK and AstraZeneca and personal fees from Novartis, Chiesi and ResMed. G.J. Criner reports personal fees from Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Broncus Medical, Chiesi, CSA Medical, Eolo, Gala Therapeutics, GSK, Helios Medical, Medtronic, Merck, Mereo BioPharma, NGM Pharmaceuticals, Novartis, Nuvaira, Olympus, Philips Respironics, Pulmonx, Respivant Sciences, The Implementation Group and Verona. He also has ownership interest in HGE Technologies. M.T. Dransfield reports personal fees from AstraZeneca, Boehringer Ingelheim, PneumRx/BTG, Quark Pharmaceuticals and GSK, grant support from the American Lung Association, Department of Defense, Department of Veterans Affairs and NIH, and contracted clinical trial support from Boehringer Ingelheim, Novartis, AstraZeneca, Yungjin, PneumRx/BTG, Pulmonx, Boston Scientific, Gala, Nuvaira and GSK. D.M.G. Halpin reports personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Pfizer and Sanofi, and non-financial support from Boehringer Ingelheim and Novartis. M.K. Han reports personal fees from AstraZeneca, GSK, Mylan, Merck and Boehringer Ingelheim and research support from Novartis and Sunovion. B.Hartley is a contingent worker with a Contract Research Organisation working on behalf of GSK and holds shares in GSK. P. Lange reports personal fees from GSK, AstraZeneca and Boehringer Ingelheim, and grant support from Boehringer Ingelheim and GSK. D.A. Lomas reports grant income, honoraria, and consultancy fees from GSK, and personal fees from Grifols, and chaired the GSK Respiratory Therapy Area Board 2012–2015. F.J. Martinez reports personal fees and non-financial support from the American College of Chest Physicians, AstraZeneca, Boehringer Ingelheim, Continuing Education, ConCert, Genentech, GSK, Inova Fairfax Health System, Miller Communications, National Society for Continuing Education, Novartis, Pearl Pharmaceuticals, PeerView Communications, Prime Communications, Puerto Rico Respiratory Society, Chiesi, Roche, Sunovion, Theravance, Potomac, University of Alabama Birmingham, Physicians Education Resource, Canadian Respiratory Network and Teva, non-financial support from ProterrixBio, Gilead, Nitto and Zambon, and personal fees from Columbia University, Integritas, MD Magazine, Methodist Hospital Brooklyn, New York University, Unity, UpToDate, WedMD/MedScape, Western Connecticut Health Network, Academic CME, Patara, PlatformIQ, American Thoracic Society, Rockpointe and France Foundation, grant support from NIH, Rare Disease Health Communications and ProMedior, and is a member of steering committees for Afferent/Merck, Biogen, Veracyte, Prometic, Bayer and Bridge Biotherapeutics. R. Wise reports personal fees from AstraZeneca/MedImmune, Boehringer Ingelheim, ContraFect, Pulmonx, Roche,

Spiration, Sunovion, Merck, Circassia, Pneuma, Verona, Bonti, Denali, Aradigm, Mylan/Theravance, Propeller Health, AbbVie and GSK, and grant support from AstraZeneca/MedImmune, Boehringer Ingelheim, Pearl Therapeutics, GSK and Sanofi-Aventis. D. Singh reports personal fees from GSK, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Genentech, Glenmark, Menarini, Mundipharma, Novartis, Peptinnovate, Pfizer, Pulmatrix, Theravance and Verona, and grant support from AstraZeneca, Boehringer Ingelheim, Chiesi, Glenmark, Menarini, Mundipharma, Novartis, Pfizer, Pulmatrix, Theravance and Verona.

References

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2020. Available from: https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf. Accessed 5th August 2020.
2. Bafadhel M, Peterson S, De Blas MA, et al. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. *Lancet Respir Med*. 2018; 6: 117-26.
3. Pascoe S, Barnes N, Brusselle G, et al. Blood eosinophils and treatment response with triple and dual combination therapy in chronic obstructive pulmonary disease: analysis of the IMPACT trial. *Lancet Respir Med*. 2019; 7: 745-56.
4. Bafadhel M, Pavord ID and Russell REK. Eosinophils in COPD: just another biomarker? *Lancet Respir Med*. 2017; 5: 747-59.
5. Long GH, Southworth T, Kolsum U, et al. The stability of blood Eosinophils in chronic obstructive pulmonary disease. *Respir Res*. 2020; 21: 15.
6. Southworth T, Beech G, Foden P, Kolsum U and Singh D. The reproducibility of COPD blood eosinophil counts. *Eur Respir J*. 2018; 52.
7. Lipson DA, Barnhart F, Brealey N, et al. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. *N Engl J Med*. 2018; 378: 1671-80.
8. Pascoe SJ, Lipson DA, Locantore N, et al. A phase III randomised controlled trial of single-dose triple therapy in COPD: the IMPACT protocol. *Eur Respir J*. 2016; 48: 320-30.
9. Prazma CM, Bel EH, Price RG, Bradford ES, Albers FC and Yancey SW. Oral corticosteroid dose changes and impact on peripheral blood eosinophil counts in patients with severe eosinophilic asthma: a post hoc analysis. *Respir Res*. 2019; 20: 83.
10. Ramirez GA, Yacoub MR, Ripa M, et al. Eosinophils from Physiology to Disease: A Comprehensive Review. *Biomed Res Int*. 2018; 2018: 9095275.

Figure. Modelled effect of FF/UMEC versus UMEC/VI and FF/VI versus UMEC/VI treatment on moderate/severe exacerbation rate, according to the best-fitting model



Rate Ratio FF/UMEC/VI vs 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)

Note: The table shows the exacerbation rate ratio for FF/UMEC/VI versus UMEC/VI for each of the five models that were applied.

*Overall best-fitting model uses eosinophils measured at randomisation.

FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol.