Blood eosinophil-guided oral prednisolone for COPD exacerbations in primary care in the UK (STARR2): a non-inferiority, multicentre, double-blind, placebo-controlled, randomised controlled trial

Sanjay Ramakrishnan, Helen Jeffers, Beverly Langford-Wiley, Joanne Davies, Samantha J Thulborn, Mahdi Mahdi, Christine A'Court, Ian Binnian, Stephen Bright, Simon Cartwright, Victoria Glover, Alison Law, Robin Fox, Adam Jones, Christopher Davies, David Copping, Richard EK Russell, Mona Bafadhel

Summary

Background Systemic glucocorticoids are recommended for use in chronic obstructive pulmonary disease (COPD) exacerbations; however, there is increased harm associated with their use. We hypothesised that the use of eosinophil biomarker-directed oral prednisolone therapy at the time of an exacerbation of COPD was effective at reducing prednisolone use without affecting adverse outcomes.

Methods The studying acute exacerbations and response (STARR2) study was a multicentre, randomised, double-blind, placebo-controlled trial conducted in 14 primary care practices in the UK. We included adults (aged ≥40 years), who were current or former smokers (with at least a 10 pack year smoking history) with a diagnosis of COPD, defined as a post-bronchodilator FEV_1/forced vital capacity ratio of less than 0·7 previously recorded by the primary care physician, and a history of at least one exacerbation in the previous 12 months requiring systemic corticosteroids with or without antibiotics. All study staff and participants were masked to study group allocation and to treatment allocation. Participants were randomly assigned (1:1) to blood eosinophil-directed treatment (BET; to receive oral prednisolone 30 mg once daily if eosinophil count was high [≥2%] or placebo if eosinophil count was low [<2%]) or to standard care treatment (ST; to receive prednisolone 30 mg once daily irrespective of the point-of-care eosinophil result). Treatment was prescribed for 14 days and all patients also received antibiotics. The primary outcome was the rate of treatment failure, defined as any need for re-treatment with antibiotics or steroids, hospitalisation for any cause, or death, assessed at 30 days after exacerbation in the modified intention-to-treat population. Participants were eligible for re-randomisation at further exacerbations (with a maximum of four exacerbations per participant). A safety analysis was conducted on all randomly assigned participants. Although designed as a superiority trial, after identification of an error in the randomisation code before data lock the study converted to show non-inferiority. An upper margin of 1·105 for the 95% CI was defined as the non-inferiority margin. This study was registered with EudraCT, 2017-001586-24, and is complete.

Findings Between Nov 6, 2017, and April 30, 2020, 308 participants were recruited from 14 general practices. 144 exacerbations (73 in the BET group and 71 in the ST group) from 93 participants (mean age 70 years [range 46–84] and mean percent predicted FEV_1 60·9% [SD 19·4]; 52 [56%] male and 41 [44%] female; ethnicity data was not collected]) were included in the modified intention-to-treat analysis. There were 14 (19%) treatment failures at 30 days post-exacerbation in the BET group and 23 (32%) in the ST group; we found a large non-significant estimated effect between BET and ST (RR 0·60 [95% CI 0·33–1·04]; p=0·070) in reducing treatment failures after a COPD exacerbation. The non-inferiority analysis supported that BET was non-inferior to ST. Frequency of adverse events were similar between the study groups; glycosuria (2/102 [2%] in BET group and 1/101 [1%] in the ST group) and hospital admission for COPD exacerbation (2/102 [2%] in BET group and 1/101 [1%] in the ST group) were the two most common adverse events in both groups. No deaths occurred in the study.

Interpretation Blood eosinophil-directed prednisolone therapy at the time of an acute exacerbation of COPD is non-inferior to standard care and can be used to safely reduce systemic glucocorticoid use in clinical practice.

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Respiratory Medicine Unit, Nuffield Department of Clinical Medicine (S Ramakrishnan MBBS, H Jeffers RGN, B Langford-Wiley RGN, J Davies RGN, S J Thulborn BSc, M Mahdi BSc, R E K Russell PhD, Prof M Bafadhel PhD), **and NIHR Oxford Biomedical Research Centre** (B Langford-Wiley, S J Thulborn, M Mahdi, R E K Russell), **University of Oxford, Oxford, UK; School of Medical and Health Sciences, Edith Cowan University, Joondalup, WA, Australia** (S Ramakrishnan); **Broadshires Health Centre, Carterton, UK** (C A'Court MBBS); **Eynsham Medical Group, Eynsham, UK** (I Binnian MBChB); **Windrush Medical Practice, Witney, UK** (S Bright MSc); **White Horse Medical Practice, Faringdon, UK** (S Cartwright MBBS, V Glover MBBS, A Law MBBS); **Montgomery House Surgery, Bicester, UK** (A Law); **Bicester Health Centre, Bicester, UK** (R Fox MBBS); **Woodlands Medical Centre, Didcot, UK** (A Jones MBBS); **Wing Surgery, Leighton Buzzard, UK** (C Davies MBBS); **Morland House Surgery, Wheatley, UK** (D Copping MBBS); **King's Centre of Lung Health, School of Immunology and Microbial Sciences, Faculty of Life Sciences and Medicine, King's**

Introduction

Systemic glucocorticoids (commonly prednisolone) are used as treatment for acute exacerbations of chronic obstructive pulmonary disease (COPD) but are not without harm.[1,2] A meta-analysis of multiple placebo-controlled trials has shown that the number of patients

College London, UK
(R E K Russell, Prof M Bafadhel)

Correspondence to:
Prof Mona Bafadhel, King's Centre for Lung Health, School of Immunology and Microbial Sciences, Faculty of Life Sciences and Medicine, London SE1 9RT, UK
mona.bafadhel@kcl.ac.uk

Research in context

Evidence before this study

International guidelines recommend using systemic glucocorticoids to treat exacerbations of COPD. A review of placebo-controlled trials of systemic glucocorticoids in exacerbations of COPD showed that the number needed to treat to prevent a treatment failure (defined as re-treatment, hospital admission, or death within 30 days) is ten, while the number needed to harm is five. These studies were primarily conducted before the widespread use of inhaled glucocorticoids in COPD care. The use of blood eosinophil count as a biomarker to guide use of inhaled glucocorticoids has transformed COPD preventative management. We searched PubMed on June 15, 2022, from database inception without language restrictions, for publications using the main search terms "COPD", "exacerbations", "biomarker", "eosinophil", and "randomised controlled trial". Two randomised controlled trials have assessed the use of a blood eosinophil count to guide systemic glucocorticoid treatment. Both studies reported that the blood eosinophil count can be used to safely reduce the use of systemic glucocorticoids in low eosinophil exacerbations, defined as less than 2% of total leucocyte count or less than 300 cells per µl, with no impact on treatment failure rates.

Added value of this study

The studying acute exacerbations and response (STARR2) study is a multicentre, double-blind, placebo-controlled randomised trial, conducted in primary care practices in the UK, which used a point-of-care testing of blood eosinophil count to guide prednisolone use in patients with an exacerbation of COPD. Our results showed that blood-eosinophil guided therapy was non-inferior to standard care with a lower cumulative oral prednisolone dose; with no clinical or statistically significant difference in lung function, symptom, or quality of life recovery, despite 30% of participants being treated with placebo for their exacerbation. Biomarker-based subgroup analysis also showed that the greatest benefit in lung function and COPD specific quality life was in participants with a high eosinophil count receiving prednisolone.

Implications of all the available evidence

Taken together with the two previous randomised trials, the STARR2 trial shows that the treatment of COPD exacerbations should be guided by a blood eosinophil biomarker. The blood eosinophil count identifies patients who would benefit from systemic glucocorticoids and helps reduce the systemic exposure and toxicity of universal prednisolone therapy. This study also suggests that the widespread use of COPD rescue packs containing prednisolone, self-initiated by patients at the onset of an exacerbation, might be driving increased harm. Health systems need to encourage systematic assessment of COPD exacerbations to provide patients with the right therapy in a precision biomarker-directed way.

needed to treat in order to prevent a treatment failure (defined as re-treatment, hospital admission, or death within 30 days) is ten, despite the number needed to harm being five.[3] Most studies have shown only short-term benefit of using glucocorticoids, particularly in reducing the risk of hospital admission from the emergency department.[3] Treatment failure is common, occurring in up to 40% of patients within 28 days of initial treatment,[4] and adverse events (eg, hyperglycaemia) occur in up to 50% of patients with even a short 5-day treatment duration.[5]

The peripheral blood eosinophil count has been shown to predict benefit from inhaled glucocorticoids, revolutionising COPD maintenance therapy,[6] and forms part of international guidelines.[7] The peripheral blood eosinophil count at the time of an exacerbation of COPD has been shown to act as a biomarker to safely reduce systemic glucocorticoids in moderate exacerbations in a proof-of-concept phase 2 trial[8] and also in patients who have been hospitalised with severe exacerbations;[9] however, blood eosinophil biomarker-directed therapy has yet to be incorporated into clinical practice. Therefore, we did a double-blind, placebo-controlled, multicentre, randomised clinical trial to test the hypothesis that eosinophil biomarker-directed oral prednisolone therapy at the time of an exacerbation of COPD can be used in patients attending primary care.

Methods

Study design and participants

The studying acute exacerbations and response (STARR2) study was a randomised, double-blind, placebo-controlled, multicentre trial conducted in 14 primary care practices in the UK. The inclusion criteria were adults (aged ≥40 years), who were current or former smokers (with at least a 10-pack per year smoking history) with a diagnosis of COPD, defined as a post-bronchodilator FEV_1/forced vital capacity ratio of less than 0·7, previously recorded by the primary care physician and a history of at least one exacerbation in the previous 12 months requiring systemic corticosteroids with or without antibiotics. The exclusion criteria were a history of atopic childhood asthma, current or past history of lung cancer or current active pulmonary tuberculosis; clinically relevant disease or disorder (past or present) which in the opinion of the investigator might put the individual at risk because of participating in the study or might influence the results of the study or the individual ability to participate in the study; any clinically relevant lung disease, other than COPD considered by the investigator to be the primary diagnosis; an alternative cause for the increase in symptoms of COPD that is unrelated to an exacerbation; a known allergy to prednisolone, doxycycline or to any of the constituents of the placebo; patients on maintenance corticosteroids; known adrenal insufficiency; currently

enrolled in another clinical trial of any investigational medicinal product and receiving an intervention as part of the trial; and pregnant and breast-feeding women. Participants were eligible to join the study at the time of exacerbation or at steady state, which was defined as no recent treatment for an exacerbation for 6 weeks. Access to primary care medical records was used to confirm these details. This design was implemented as recommended by the patient panel representatives during trial design.

This study was approved by the Fulham London Research Ethics Committee (17/LO/1135) and the National Health Research Authority. All participants provided informed written consent.

Randomisation and masking

Patients registered at the participating general practices with a diagnosis of COPD were screened for eligibility by the general practitioner and were invited to participate in the study. A participant with an exacerbation of COPD could be screened for randomisation by directly contacting the study team or presenting to the general practice with symptoms consistent with a COPD exacerbation. Eligibility for randomisation was confirmed by the primary care physician who was the nominated principal investigator. Confirmation of randomisation eligibility activated the initiation of study protocols and randomisation by the study nurses. Participants were deemed eligible for randomisation if, in the opinion of the primary care clinician, the clinical review confirmed an exacerbation of COPD that needed systemic treatment with prednisolone. Participants were eligible for re-randomisation if they had another exacerbation during the study period at a maximum of four times and were free from an exacerbation in the preceding 6 weeks. Participants were randomly assigned (1:1) to blood eosinophil-directed treatment (BET) or to standard care treatment (ST) via a centralised computer randomisation service (RRAMP), provided by the Oxford Clinical Trials Research Unit. Randomisation was stratified for the blood eosinophil count (<2%, 2 to <4%, ≥4%), percentage FEV_1 at baseline (<50% or ≥50% predicted), and the number of exacerbations in the previous 12 months (<2 or ≥2 exacerbations). We used variable block sizes for randomisation, completed by a statistician in the clinical trials unit who was not masked to the study. All study staff and participants were masked to study group allocation and to treatment allocation.

Procedures

All study visits occurred at the primary care practice. Participants were seen at the following visits: steady state (baseline); exacerbation (randomisation); and at day 14, day 30, and day 90 after exacerbation. At the baseline visit, demographics, medication, and exacerbation history was recorded. At each visit, participants had post-bronchodilator spirometry and completed patient-reported questionnaires (Medical Research Council dyspnoea scale; visual analogue score [VAS]; COPD Assessment Test [CAT]; the Hospital Anxiety and Depression Scale [HADS]; and the EuroQol 5D). Participants also had a point-of-care measurement of blood eosinophils and C-reactive protein using the HemoCue WBC DIFF (Radiometer; Copenhagen, Denmark) and QuikRead go CRP (Una Health; Stoke-on-Trent, UK) analyser, respectively. The point of care required up to three drops of blood from a finger prick (maximum of ten drops) for each test. The HemoCue WBC DIFF is able to measure a 5-point differential absolute cell count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes) and a total leukocyte count within 2 min of sampling, using photometric technology with internal calibration. This technology has been validated in patients with COPD.[10] The QuikRead go CRP analyser uses photometric and turbidimetric technology validated in patients with COPD exacerbations.[11] The point-of-care blood eosinophil count was only used at the randomisation visit.

After exacerbation, participants were also asked to complete a daily VAS diary for symptoms of cough, dyspnoea, wheeze, sputum production, and sputum purulence for 30 days, for assessment of symptoms and recovery.

At the time of randomisation, if the point-of-care blood eosinophil count was high (≥2%), participants in the BET group received oral prednisolone (Tiofarma BV, Oud-Beijerland, Netherlands) 30 mg once daily, and if the point-of-care blood eosinophil count was low (<2%), participants received matched placebo instead. Participants in the ST group received oral prednisolone 30 mg once daily irrespective of the point-of-care blood eosinophil count. All participants took the investigational medicinal product (ie, prednisolone or matched placebo) once a day for 14 days as per national guidance at the time of protocol development.[12] All participants were also prescribed doxycycline (supplied by the local pharmacy) at a dose of 200 mg once daily for 7 days as per recommendation from the ethics committee review. At the time of the study, doxycycline was the antibiotic recommended for use to treat COPD exacerbations by national guidelines.[12] Adherence to investigational medicinal product (defined as at least 12 days) and doxycycline (defined as at least 6 days) was checked at the day 14 study visit.

For more on **RRAMP** see https://it.octru.ox.ac.uk/

Outcomes

The primary outcome, based on unique exacerbation episodes, was the proportion of treatment failure—defined as exacerbations needing re-treatment, hospital admission, or death—at 30 days (and at 90 days as a separate endpoint). Retreatment was defined as the need for retreatment with systemic glucocorticoids with or without antibiotics. Secondary outcomes were health-related quality of life (CAT and EuroQol 5D), FEV_1, and VAS respiratory symptoms (cough, wheeze,

breathlessness, sputum production, and sputum colour). We also report total VAS score as the sum of the individual VAS domains. EuroQol 5D and frequency of moderate and severe exacerbations in the following 12 months will be reported in a future manuscript. Time to treatment failure (composite outcome including patients requiring prednisolone or antibiotics, or both) was assessed post-hoc.

Statistical analysis

All analyses were prespecified. Descriptive statistics were used for baseline variables between the BET and ST groups. For the primary outcome (assessed in the modified intention-to-treat population, which included all participants randomised after the randomisation error was detected), the proportion in each category were reported for each treatment group and χ^2 tests were used for comparison. Continuous secondary outcomes were analysed using a mixed-model for repeated measures, with inclusion of a random effect for each exacerbation and a fixed interaction term between treatment group and study visits. Each exacerbation that led to a randomisation was treated as an independent event.[13–15] All tests were done at a 5% two-sided significance level and all comparative outcomes are presented as summary statistics and reported in accordance with the CONSORT statement.[16] Analyses were performed using R software version 4.2.0. The R packages *lme4* (version 1.1)[17] and *emmeans* (version 1.8.1)[18] were used for linear mixed modelling. Further details are shown in the appendix (47–66). Relative risk (RR) was defined as the risk of any treatment failure in the biomarker-directed treatment group compared with the risk of any treatment failure in the standard care group. A Cox proportional hazard model was used to estimate the hazard ratio (HR). HR was defined as the odds that an individual in either group had a treatment failure first compared with the other group. 95% CIs were reported for all outcomes. For the primary outcome, imputation was used for missing data. For time to treatment failure analyses, participants were censored if they were lost to follow-up before their first episode of treatment failure. For all other secondary outcomes, they were assumed to be missing at random within the linear mixed models and no imputation was performed.

See Online for appendix

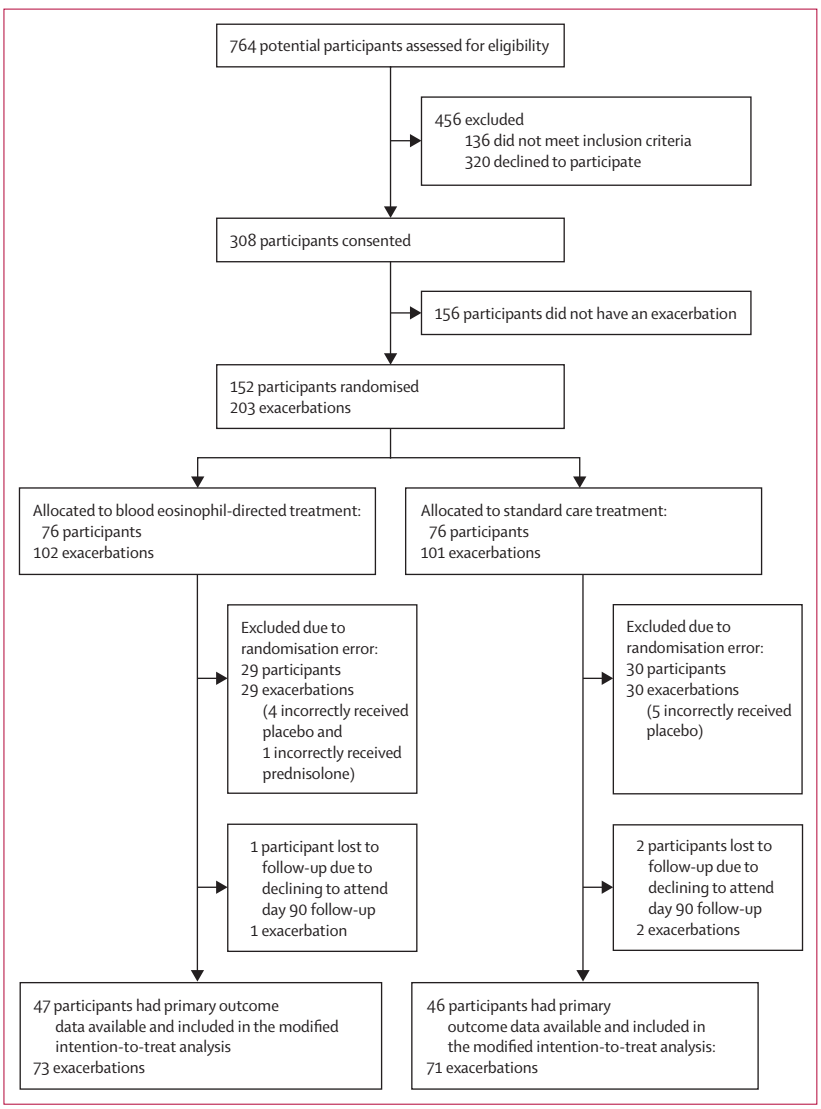


Figure 1: **Trial profile**
At each stage, the number of participants and number of exacerbations are included. Each unique participant could contribute more than one unique exacerbation to the study. Participants were eligible for re-randomisation if they had another exacerbation during the study period at a maximum of four and were free from an exacerbation in the preceding 6 weeks. The number of participants that had one, two, three, and four exacerbations was 54, 29, nine, and one, respectively. IMP=investigational medicinal product.

The effect rate and size were estimated from previous studies.[3,8] A sample size of 182 participants (91 per group) had an 80% power and 5% two-sided significance to detect a 50% reduction in treatment failure rate from an expected rate of 40% in the ST group to 20% in the BET group at 30 days. The study was terminated on April 30, 2020, due to the COVID-19 pandemic.

On June 28, 2018, an error was detected in the randomisation RRAMP software, affecting all of the randomisations since the study start date (n=60). This error was detected by the randomisation provider at the clinical trials unit, after demonstration of the software to other investigators (outside of this study) interested in using the RRAMP software. When the software was unable to process the stratification, it reverted to the underlying block randomisation, randomly choosing between BET and ST groups and allocating the next

available investigational medicinal product at the study site. As a consequence of this error, some patients with a high blood eosinophil count allocated to BET received placebo, some patients with a low blood eosinophil count allocated to BET received prednisolone, and some patients allocated to ST received placebo. The study was immediately paused due to this serious protocol breach and the study investigators, participants, study sponsor, ethics committee, and the National Health Research Authority were notified. No participants were unmasked from treatment allocation after discussion with the regulators and the ethics committee. The trial resumed recruitment after the coding error was rectified on Aug 14, 2018.

Due to the serious errors in randomisation and the resultant reduction in power as a superiority trial, the trial was converted to show non-inferiority before data lock (Feb 22, 2022). Using the same assumptions made for the superiority analysis calculation, a sample size of 106 (53 exacerbations in each group) was required to show that the BET is non-inferior to ST. A preserved ratio of 75% was used to determine the non-inferiority margin,[19] with a 95% CI upper margin of 1·105, from previous literature examining using this study design in COPD exacerbations.[3] For BET to be considered non-inferior, the intervention had to obtain at least 75% of the benefit obtained against current standard care (ie, prescribing prednisolone for all exacerbations). All further statistical analysis were assessed in the modified intention-to-treat (mITT) population, which included only correctly randomised participants. The safety analyses were conducted on all randomly assigned participants. No data monitoring committee was used. This study was registered with EudraCT, 2017-001586-24 (NCT04458636).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From Nov 6, 2017, to April 30, 2020, 764 participants were assessed for eligibility, of whom 308 participants consented and were enrolled from 14 primary care practices and assigned BET (n=102) or ST (n=101; figure 1). Following exclusion due to randomisation error, 144 exacerbations were randomised from 93 participants (mean age 70 years [range 46–84]; and mean percent predicted FEV_1 60·9% [SD 19·4]; 52 [56%] male and 41 [44%] female; Ethnicity data were not captured). The number of participants that had one, two, three, and four exacerbations was 54, 29, nine, and one, respectively. 54 (58%) of 93 participants were already being treated with inhaled glucocorticoids and the majority of participants were former smokers (70 [75%]), with a mean smoking history of 55 (IQR 10–290) pack years. Participant characteristics at baseline were largely similar between the study groups (table 1), although the participants randomly assigned to BET had more current smokers, more heart failure, and higher VAS symptoms of

	Standard care treatment group (n=46)	Blood eosinophil-directed group treatment (n=47)
Sex		
Female	20 (43%)	21 (45%)
Male	26 (57%)	26 (55%)
Mean age, years	70 (range 46–83)	70 (range 50–84)
Smoker status		
Current smoker	7 (15%)	16 (34%)
Former smoker	39 (85%)	31 (66%)
Mean smoked pack years	50 (range 10–140)	60 (range 10–175)
Comorbidity		
Any	45 (98%)	46 (98%)
Hypertension	23 (50%)	22 (47%)
Gastro-oesophageal reflux	16 (35%)	20 (43%)
Depression	13 (28%)	17 (36%)
History of malignancy	7 (15%)	10 (21%)
Ischaemic heart disease	11 (24%)	8 (17%)
Diabetes	4 (9%)	7 (15%)
Atrial fibrillation	7 (15%)	7 (15%)
Osteoporosis	2 (4%)	4 (9%)
Cerebrovascular disease	1 (2%)	1 (2%)
Heart failure	0	4 (9%)
BMI, kg/m^2	27·9 (6·2)	28·2 (6·2)
FEV_1, L	1·60 (0·62)	1·51 (0·62)
FEV_1 % predicted	61·0 (19·4)	60·8 (19·2)
FEV_1/FVC	0·55 (0·10)	0·56 (0·10)
COPD Assessment Test score	14 (7)	16 (7)
VAS total, mm*	119 (95)	162 (118)
VAS cough, mm	24 (21)	34 (26)
VAS dyspnoea, mm	29 (25)	40 (25)
VAS sputum production, mm	22 (23)	28 (28)
VAS sputum purulence, mm	20 (22)	28 (29)
VAS wheeze, mm	23 (23)	31 (27)
Median EuroQOL level sum score	6 (IQR 5–8)	7 (IQR 5–8)
Median hospital anxiety and depression score	9 (IQR 5–13)	12 (IQR 5–16)
Median number of previous exacerbations in past 12 months	2 (IQR 1–3)	2 (IQR 1–3)
Treatment		
On long-acting muscarinic antagonist therapy	28 (61%)	27 (57%)
On long-acting β2-receptor agonist therapy	30 (65%)	26 (55%)
On inhaled glucocorticoid therapy†	28 (61%)	26 (55%)
Beclomethasone dipropionate equivalent, µg	567 (578)	572 (576)
Median Medical Research Council score	2 (IQR 2–3)	3 (IQR 2–3)
Geometric mean leukocytes (95% CI), 10^9 cells per L	7·02 (6·49–7·47)	6·99 (6·85–8·18)
Geometric mean neutrophils (95% CI), 10^9 cells per L	4·24 (3·83–4·66)	4·24 (4·06–4·98)
Geometric mean eosinophils (95% CI), 10^9 cells per L	0·16 (0·14–0·20)	0·16 (0·14–0·20)
Median C-reactive protein, g/L	5 (IQR 2–8)	6 (IQR 2–10)

Data are n (%) or mean (SD) unless otherwise stated. COPD=chronic obstructive pulmonary disease. FVC=forced vital capacity. VAS=visual analogue scale. *VAS total is the total of each of the VAS domains. †Includes patients on any inhaled corticosteroid formulation.

Table 1: **Baseline characteristics (modified intention-to-treat population)**

cough and breathlessness at baseline compared with participants allocated to ST. 19 (20%) of 93 participants treated with BET or ST had a eosinophil count of more than $0·3\times10^9$ cells per L (300 cells per µL) at baseline.

Participants met adherence criteria to IMP for 68 (93%) of 73 reported exacerbations in the BET group and 64 (91%) of 71 in the ST group. In both groups, the geometric mean point-of-care eosinophil count was $0·16\times10^9$ cells per L (95% CI 0·14–0·20). There were no statistically significant differences in baseline characteristics in participants reaching the primary outcome compared with those who did not (data not shown) and there were no missing data for the primary outcome. In the analysis for the primary outcome at day 30, there were 37 treatment failures in the mITT population; of 73 exacerbations there were 14 (19%) treatment failures in the BET group and of 71 exacerbations there were 23 (32%) treatment failures in the ST group, with 40% fewer treatment failures in the BET group compared with ST (RR 0·60 [95% CI 0·33 to 1·04]; p=0·070). The median time to treatment failure could not be estimated as neither group reached the 50% treatment failure threshold. A Cox proportional hazard model showed that the HR for treatment failure at day 30 was 0·71 (95% CI 0·41–1·24; p=0·200) in the BET group compared with ST (figure 2A). Analysis for the primary outcome showed that BET was non-inferior to ST as the upper limit of the 95% CI for relative risk did not cross the predetermined non-inferior line of 1·105 (figure 2B).

In the BET group, there were 48 (66%) exacerbations that received prednisolone compared with 71 (100%) exacerbations that received prednisolone in the ST group. As expected, this study design was associated with a 33% reduction in prednisolone prescribing in the BET group compared with the ST group. To account for the protocolised difference in prednisolone dosing, we assessed the additional doses of prednisolone prescribed to participants who reached the primary outcome and those who had additional retreatment in the 30 days after randomisation. The cumulative treatment failure prednisolone dose was 1620 mg (range 90–420 mg per patient requiring prednisolone) in the BET group versus 3450 mg (range 150–420 mg per patient requiring prednisolone) in the ST group, respectively.

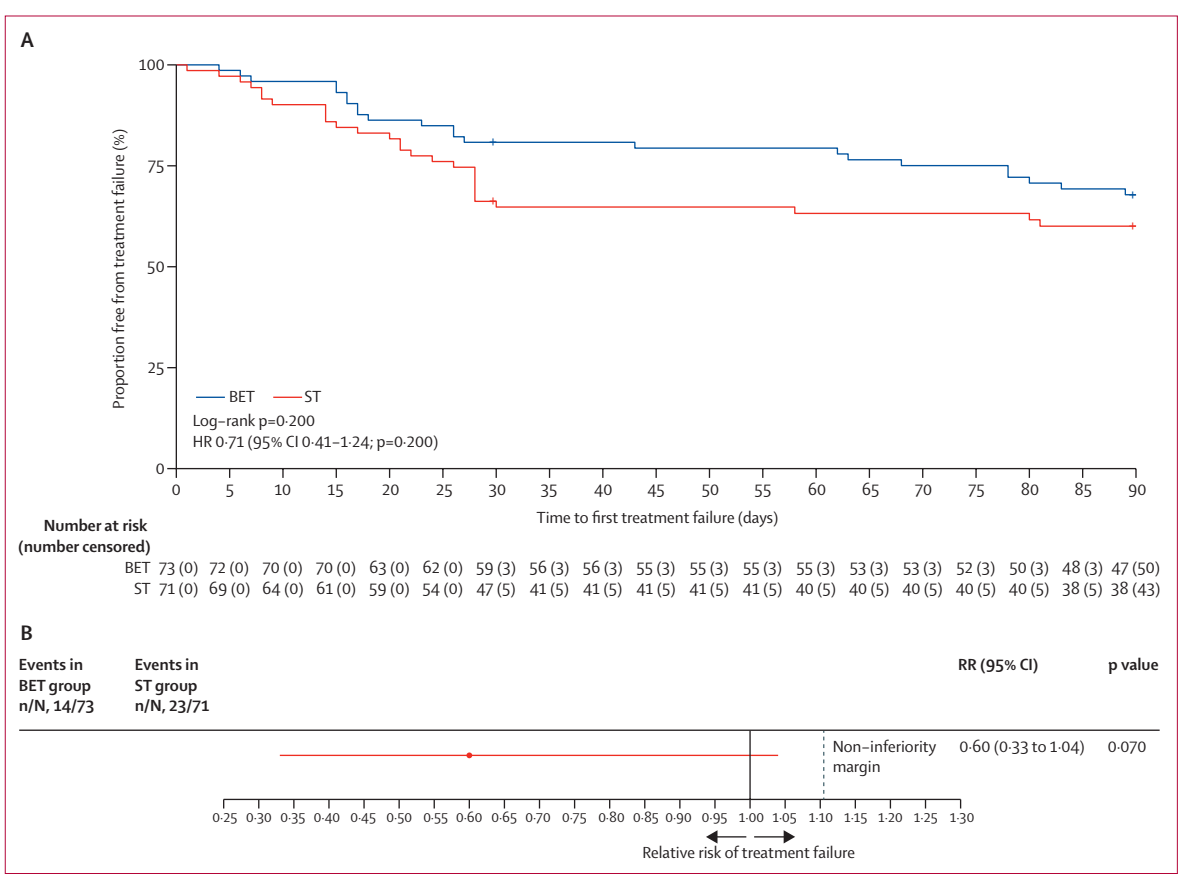


Figure 2: **Time to treatment failure between study groups (A) and primary outcome relative risk (B)**
(A) Data shown are for the number of treatment failures after randomisation. Each participant could have had more than one treatment failure. Time to first event is reported. 59 treatment failures occurred out of 144 randomised exacerbations at day 90. (B) Dashed line represents the pre-determined non-inferiority margin set at a 75% preserved ratio. BET=blood eosinophil-directed treatment. COPD=chronic obstructive pulmonary disease. HR=hazard ratio. ST=standard care treatment. VAS=visual analogue scale.

With regard to the secondary outcomes, at day 14 there was no significant difference in the improvement of post-bronchodilator FEV_1, CAT, or VAS symptoms between the BET and ST groups (EuroQOL was not reported; table 2). At 30 days, CAT did not return to baseline in the ST group and was significantly worse (–2 [95% CI –4 to –1]; p=0·0060) than BET, indicating incomplete recovery (appendix pp 3, 10).

All 144 exacerbations in both groups were analysed together for the subgroup analysis according to the eosinophil endotype. The majority of exacerbations (n=94 [65%]) were in the high (≥2%) eosinophil category (appendix p 4). There were more male participants with exacerbations associated with high eosinophil count compared with those with exacerbations associated with low eosinophil count (66% *vs* 38%, respectively; (appendix p 4). There were similar numbers of day 30 treatment failures in exacerbations associated with low (<2%) eosinophil count and high eosinophil count (15 [30%] of 50 in the low eosinophil group *vs* 22 [23%] of 94 in the high eosinophil group; RR 1·24 [95% CI 0·75–1·94]; p=0·462; appendix p 4). At day 14, exacerbations with high eosinophil count treated with prednisolone had a better response in FEV_1 (mean improvement 0·19 L [95% CI 0·13 to 0·25]) compared with exacerbations with low eosinophil count treated with placebo (FEV_1 of 0·05 L [–0·17 to 0·07]; post-hoc Tukey's test p<0·0001) and in exacerbations with low eosinophil count treated with prednisolone (0·09 L [–0·26 to 0·07]; post-hoc Tukey's test p=0·0026; table 3; appendix p 8). CAT, FEV_1, and VAS symptoms returned to baseline in the exacerbations with low eosinophil count and were not clinically or significantly different between exacerbations with low eosinophil count treated with prednisolone or placebo (table 3; figure 3). There was an incomplete resolution at day 30 of CAT, FEV_1, and VAS (total, dyspnoea, and wheeze) in exacerbations with high eosinophil count treated with prednisolone (appendix p 6). There were fewer treatment failures in exacerbations with low eosinophil count treated with placebo compared with exacerbations with low eosinophil count treated with prednisolone at day 30 (four [16·7%] *vs* 11 (42%); RR 0·47 [95% CI 0·18–0·99]; p=0·048). Cox proportional hazard modelling did not show statistically significant differences between groups (figure 3). In exacerbations with low eosinophil count treated with prednisolone, the number needed to harm was six, compared with exacerbations with low eosinophil count treated with placebo.

The number of adverse events in the study was low and similar between both study arms (appendix p 7). Glycosuria (two participants in BET and one participant in ST) and hospital admission for COPD exacerbation (two participants in BET and one participant in ST) were the two most common adverse events in both groups. No deaths occurred in the study. One participant in the BET group discontinued treatment due to a headache.

	Standard care treatment group (n=71)	Blood eosinophil-directed group (n=73)	p value
Change in COPD Assessment Test score	7 (6 to 8)	8 (6 to 10)	0·271
Change in FEV_1, L	0·14 (0·07 to 0·21)	0·17 (0·10 to 0·24)	0·548
Change in VAS total, mm*	126 (99 to 152)	127 (103 to 150)	0·971
Change in VAS cough, mm	25 (19 to 31)	26 (20 to 32)	0·828
Change in VAS dyspnoea, mm	22 (15 to 29)	23 (17 to 29)	0·772
Change in VAS sputum production, mm	26 (19 to 33)	24 (18 to 30)	0·726
Change in VAS sputum purulence, mm	26 (18 to 34)	25 (19 to 31)	0·857
Change in VAS wheeze, mm	27 (21 to 33)	26 (21 to 32)	0·933
Geometric mean change in leukocytes (95% CI), 10^9 cells per L	2·7 (1·5 to 3·9)	1·7 (0·9 to 2·5)	0·167
Geometric mean change in neutrophils (95% CI), 10^9 cells per L	1·8 (0·9 to 2·7)	1·3 (0·7 to 1·9)	0·313
Geometric mean change in eosinophils (95% CI), 10^9 cells per L	–0·2 (–0·3 to –0·1)	–0·2 (–0·2 to –0·1)	0·535
Median Change in C-reactive protein, g/L	–10 (IQR –32 to –4)	–5 (IQR –15 to –3)	0·058

Data are mean (95% CI) unless otherwise stated. A negative value in FEV_1, COPD Assessment Test score, and VAS indicates worsening (reduction). COPD=chronic obstructive pulmonary disease. VAS=visual analogue scale. *VAS total is the total of each of the VAS domains.

Table 2: **Secondary analysis of the difference in clinical, physiological, and biological characteristics after treatment allocation between exacerbation (randomisation) and 2 weeks of treatment (day 14 follow-up visit) in modified intention-to-treat population**

Discussion

We have shown in a large, multicentre, clinical trial in UK primary care that using eosinophil point-of-care testing at the time of an exacerbation to direct prednisolone treatment is not associated with an increase in harm compared with standard care. Specifically, there was no increase in treatment failures (primary outcome) nor worsening in symptoms or lung function (secondary outcomes) using BET compared with ST at the time of an acute exacerbation. In this study, we demonstrated non-inferiority using BET compared with ST and observed a large estimated treatment effect. We were able to demonstrate that there was a reduction in prednisolone prescriptions and a lower cumulative dose of prednisolone in the BET group compared with the ST group. Finally, we have shown that in patients with exacerbations and low eosinophil count there was no significant difference in treatment failures, nor resolution of symptoms or lung function whether treated with prednisolone or placebo.

Systemic glucocorticoids, such as prednisolone, are the mainstay of treatment for exacerbations of COPD, with a number needed to treat of ten to reduce one treatment failure.[3] This universally applied treatment has been given on the basis of the short-term effect of systemic glucocorticoids on reduced length of hospital stay,[20] despite more patients being harmed than not[3,5] and with worrisome effects of prednisolone on morbidity[2] and mortality.[1] We believe that the current paradigm of treating all COPD exacerbations with systemic glucocorticoids is thus out of date,[7] and we now have further evidence that supports that current clinical practice should change. Unlike other medical disciplines,

	Low (<2%) eosinophil count + placebo (n=24)	Low (<2%) eosinophil count + prednisolone (n=26)	High (≥2%) eosinophil count + prednisolone (n=94)	p value
Change in COPD Assessment Test score	−2 (−6 to 2)	7 (5 to 9)	9 (7 to 10)	0·120
Change in FEV_1, L	−0·05 (−0·17 to 0·07)	−0·09 (−0·26 to 0·08)	0·19 (0·13 to 0·25)	0·124*
Change in VAS total, mm†	100 (61 to 139)	117 (74 to 160)	137 (115 to 158)	0·265
Change in VAS cough, mm	23 (12 to 33)	26 (16 to 37)	26 (21 to 32)	0·826
Change in VAS dyspnoea, mm	22 (12 to 32)	18 (5 to 30)	25 (19 to 30)	0·476
Change in VAS sputum production, mm	15 (6 to 24)	26 (13 to 39)	28 (22 to 33)	0·101
Change in VAS sputum purulence, mm	20 (9 to 30)	27 (14 to 39)	27 (21 to 33)	0·490
Change in VAS wheeze, mm	20 (13 to 28)	20 (13 to 30)	30 (24 to 35)	0·105
Geometric mean Change in leukocytes (95% CI), 10^9 cells per L	−0·4 (−1·6 to 0·7)	2·5 (0·8 to 4·3)	2·9 (2·0 to 3·8)	0·003
Geometric mean Change in neutrophils (95% CI), 10^9 cells per L	−0·6 (−1·4 to 0·3)	1·3 (−0·2 to 2·8)	2·2 (1·5 to 2·8)	0·001*
Geometric mean Change in eosinophils (95% CI), 10^9 cells per L	0·0 (−0·1 to 0·1)	0·0 (−0·1 to 0·1)	−0·3 (−0·4 to −0·2)	<0·001*
Median Change in C-reactive protein, g/L	−5 (−9 to −4)	−20 (−50 to −6)	−8 (−17 to −3)	0·058

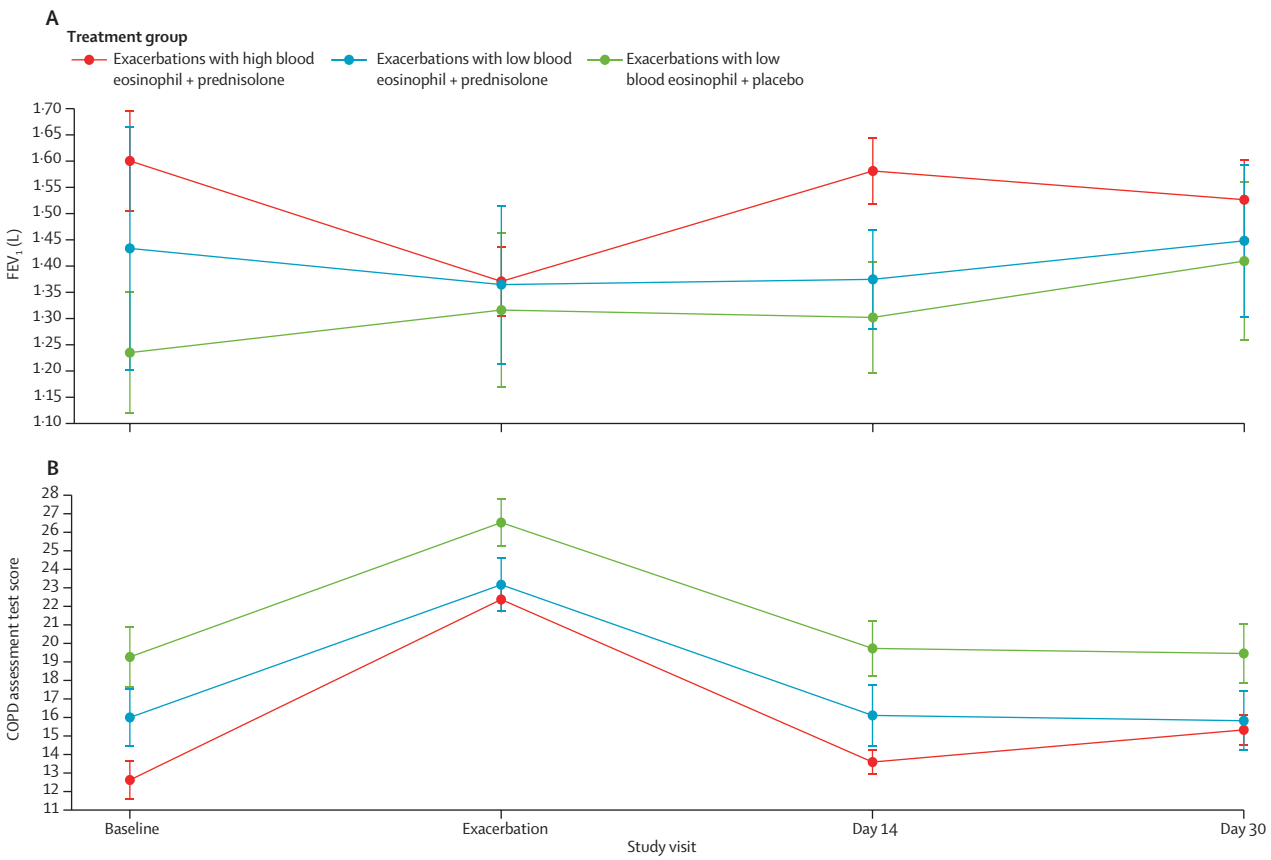
All data presented as mean (95% CI) unless otherwise stated. A negative value in FEV_1, COPD Assessment Test score, and VAS indicates worsening (reduction). All normally distributed data were analysed using a one-way analysis of variance (ANOVA) statistical test. Non-normally distributed data were assessed with the Kruskal-Wallis test. COPD=chronic obstructive pulmonary disease. VAS=visual analogue scale. *Post-hoc Tukey's test showed a statistically significant difference between the group with high (≥2%) eosinophil count treated with prednisolone compared with both other groups (appendix p 8). †VAS total is the total of each of the VAS domains.

Table 3: **Change in clinical, physiological, and biological characteristics between exacerbation and day-14 follow-up according to blood eosinophil count and treatment allocation (modified intention-to-treat population)**

the field of respiratory medicine has not achieved meaningful reductions in the use of systemic glucocorticoids,[21] increasing the risk to patients of severe life-limiting side-effects and co-morbidities.[2] Notably, primary care physicians and pulmonologists now account for the majority of prednisolone prescriptions in the UK.[22] Furthermore, the evidence that has established universal prednisolone prescription in COPD guidelines comes from fewer than 1000 patients entered into placebo-controlled trials, and was generated before the widespread availability and use of inhaled dual bronchodilators and glucocorticoids in COPD.[7]

In this study, we have shown that in patients allocated standard care there was an incomplete resolution of lung function and quality of life changes after treatment with prednisolone for an exacerbation of COPD. Moreover, 30 days after the exacerbation, the health status of patients, as measured by CAT, was significantly worse in patients allocated standard care, compared with patients allocated biomarker-directed care. This finding has important implications. The evidence base for the use of systemic corticosteroids at the time of an exacerbation of COPD is based on the short-term benefits on improvements in lung function at 72 h,[20] but to our knowledge no evaluation of changes in quality of life has ever been shown. The finding that prednisolone therapy unselectively can result in worsening in patients is similar to that in a previous study evaluating eosinophil biomarker-directed prednisolone.[8] Furthermore, our symptom-based data, measured by VAS, showed that there were no differences in symptoms between patients who had treatment failures and those who did not have treatment failures and that there was no symptom able to predict the need for prednisolone or success of the BET group over ST. This finding is at odds with the long-held view that exacerbations with predominant wheeze or breathlessness would benefit from systemic glucocorticoids, highlighting that symptoms alone are not sufficient to predict who will respond to treatment or will have treatment failure.

Our analysis of the biomarker-stratified group of this study is also revealing. Measuring a point-of-care blood eosinophil count at time of exacerbation was practical in the setting of primary care. The within-participant repeatability of percentage blood eosinophil counts has already been shown to be good, highlighting reproducible exacerbation endotypes.[8,23] There were numerically more treatment failures in exacerbations with low eosinophil count receiving prednisolone compared with those receiving placebo, with a number needed to harm of six for this group. Importantly, there was improvement of lung function, quality of life, and symptoms in exacerbations with low eosinophil count independent of whether placebo or prednisolone was prescribed. We showed that the biggest improvement in lung function after treatment occurred in exacerbations with high eosinophil count treated with prednisolone. Furthermore, we also found that CAT, FEV_1, and VAS in exacerbations with high eosinophil count did not return to baseline values at day 30, without change in baseline inhaled treatment, which was consistent with other research that showed that the eosinophilic COPD endotype is associated with increased risk of disease progression and increased number of exacerbations.[6] These findings replicate findings from a previous placebo-controlled trial,[8] in particular the demonstration that there is a different response to prednisolone treatment based on the underlying inflammation at time of the exacerbation. These findings also indicate that this inflammatory



Number at risk (number censored) Treatment group																			
Exacerbations with high blood eosinophil + prednisolone	94 (0)	92 (0)	90 (0)	89 (0)	84 (0)	79 (0)	71 (6)	64 (6)	64 (6)	63 (6)	63 (6)	63 (6)	62 (6)	61 (6)	60 (6)	60 (6)	59 (6)	55 (6)	54 (60)
Exacerbations with low blood eosinophil + placebo	24 (0)	24 (0)	22 (0)	22 (0)	20 (0)	20 (0)	20 (1)	19 (1)	19 (1)	19 (1)	19 (1)	19 (1)	18 (1)	18 (1)	18 (1)	18 (1)	17 (1)	17 (1)	17 (18)
Exacerbations with low blood eosinophil + prednisolone	26 (0)	25 (0)	22 (0)	20 (0)	18 (0)	17 (0)	15 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (15)

Figure 3: **FEV_1, COPD assessment test score, and time to treatment failure according to blood eosinophil count at randomisation and allocated treatment in the modified intention-to-treat population**

(A) Data were corrected for participants that were retreated with prednisolone after randomisation by at least 1 day, to account for any treatment effect outside of the randomisation schedule. Error bars indicate the standard error of the mean. (B) Data were corrected for participants that were retreated with prednisolone after randomisation by at least 1 day. Error bars indicate the standard error of the mean. A higher CAT score indicates worse COPD-related quality of life. (C) Time to treatment failure. COPD=chronic obstructive pulmonary disease. VAS=visual analogue scale. HR=hazard ratio.

endotype of COPD is associated with greater detriment, while the inflammation persists; and this finding might add further to the evidence base following on from the BOREAS study.[24]

The STARR2 trial findings also questions the widely held view that self-treatment with rescue packs is useful in COPD exacerbation treatment. We have shown that, in a proportion of patients being concurrently treated with antibiotics, prednisolone therapy is doing harm and that it is not clinically different from placebo therapy in its therapeutic effect. There is a nihilistic view in the management of patients with COPD;[25] evidence shows that self-management plans neither reduce health-care utilisation nor mortality.[26] Furthermore, in a study investigating a self-tailored management plan, a large number of events leading to rescue packs were associated with symptoms suggestive of heart failure, ischaemic heart disease, and anxiety;[27] and it is worth noting that in our study population comorbidity frequency was high. No other field of medicine advocates for self-treatment of life-threatening events. For example, patients with chest pain are all advised to call emergency services, but most patients with COPD are expected to manage and self-treat potentially life threatening exacerbations. Further studies investigating rescue pack use at the time of an exacerbation should take into account the underlying inflammatory endotype.

An important limitation in this study was the error in the randomisation code detected after 60 randomisations. This outcome reduced the statistical power of the trial, for it to be completed as a superiority study. To overcome this limitation, before data-lock, we pre-determined a stringent non-inferiority margin and completed all analyses in an mITT population. The mITT population provides an unbiased view of the true effect size. We were able to show that blood eosinophil-guided therapy is indeed non-inferior to standard care and had a large estimated treatment effect, with a 40% reduction in treatment failures using this study design. Of course, the prespecified 75% threshold for non-inferiority is arbitrarily defined[19] and a more conservative approach, set at 90% preserved ratio, for example, would have remained to reach the non-inferiority margin in the mITT analysis. We argue that achieving 75–90% of the benefit using placebo over a potentially harmful treatment such as prednisolone is a laudable outcome and something that should be implemented. The reductions in total additional prednisolone used to treat patients who had treatment failure with initial treatment is further evidence that accurate phenotyping of exacerbations, using readily accessible tests (eg, point-of-care eosinophil count) can quickly reduce harm in this patient cohort. Furthermore, in clinical practice we would argue that if a patient does not receive prednisolone therapy in the first instance (by virtue of biomarker-directed therapy or self-management) any worsening of symptoms would lead to close evaluation of the exacerbation and presumed follow-on prescription of prednisolone therapy. Another important limitation is the relatively low number of exacerbations associated with a low eosinophil count. This finding is not consistent with secondary care and hospital datasets.[28,29] This finding might have arisen because the point-of-care eosinophil results are reported to 1 decimal place and thus associated with rounding bias.[10] This finding potentially reduced the ability of the study design to detect a bigger impact on the primary and secondary outcomes. Any future studies would need to recruit an equal number of exacerbations that were associated high and low eosinophil counts or limit the study only to participants with a low blood eosinophil count at exacerbation. We also acknowledge that blood eosinophil counts also display a diurnal pattern in variability, but this has been mainly studied in healthy controls and patients with asthma.[30,31] We did not record the time of day the point-of-care blood test was performed in the study but we can confirm that all randomisations took place during normal office working hours (9 am to 4 pm). Whilst the allocation of prednisolone or placebo in the biomarker-directed therapy study group relied on the relative eosinophil count, we cannot be certain whether the absolute count would have changed the study outcome. The relative count is likely to indicate important information about other cells at the time of an exacerbation and has been derived from the only study to ever look at sensitivity and specificity of airway eosinophilic exacerbations.[23] Most participants randomised in the study were former smokers, which could reduce the validity of the findings in current smokers. Finally, the length of treatment with prednisolone of 14 days used in the study was the standard of care at the time this study was proposed and was approved by the funder. During the study period, national and international guidelines moved towards recommending shorter courses of treatment for COPD exacerbations.[12] We acknowledge that the longer courses of treatment in our study might have increased the degree of harm from the prednisolone intervention, but this does rule out any additional benefit in preventing treatment failure by using a longer course of treatment.

To conclude, we have shown that blood eosinophil-directed prednisolone therapy at the time of an acute exacerbation of COPD is not associated with increased rate of treatment failures and can safely reduce systemic glucocorticoid use. We recommend that these findings should be implemented into clinical practice.

Contributors

MB, HJ, JD, BLW, CAC, IB, SB, SC, VJ, AL, AJ, CD, DC, and RF were responsible for participant recruitment. HJ, JD, and BLW did all the study assessments. MM and SJT were responsible for processing study samples. SR and REKR were responsible for data analysis. SR, REKR, and MB have accessed and verified the data. The study was conceived, designed, set-up, analysed and interpreted by MB. All authors had access to the complete data, were responsible for writing of the manuscript, and accept responsibility for the manuscript.

Declaration of interests

SR reports personal salary support from the National Institute for Health and Care Research, an unrestricted research grant from AstraZeneca to his institution, and speaker fees and conference travel

support from AstraZeneca, all outside of the submitted work. MB reports salary support and direct funding for the study from the National Institute for Health and Care Research through a named fellowship. Outside of the submitted work, MB reports research grant funding paid to her institution from AstraZeneca, Roche, the European Respiratory Society, and Asthma + Lung UK. Outside of the submitted work, she also reports consulting fees from AstraZeneca, Sanofi, GSK, and Areteia, paid to her and her institution. She has received conference travel support from Chiesi. She has a leadership and board roles at the British Thoracic Society, AlbusHealth, and ProAxsis. All other authors declare no competing interests.

Data sharing

De-identified individual participant data and a data dictionary defining each field in the set can be made available to others on approval of a written request to the corresponding author. The request will be evaluated by a committee formed by a subset of co-authors to determine the research value. A data sharing agreement will be needed.

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