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Multicentre double-blind randomised controlled trial of systematic corticosteroid therapy in patients with acute exacerbations of chronic obstructive pulmonary disease admitted to hospital with higher eosinophil levels: the ECHO protocol

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ABSTRACT

Introduction Corticosteroid is one of the most commonly used medications in patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD). The increasing understanding of these side-effects of systematic corticosteroids and their better response to treatment among patients with COPD with higher blood eosinophil counts has led to an interest in a more targeted approach to systematic corticosteroid treatment. However, there is a lack of evidence from high-quality randomised controlled trial (RCT) studies about whether initial systematic corticosteroids should be given to patients with AECOPD with elevated eosinophilia. The aim of the present research was to test this hypothesis.

Methods and analysis This is a multicentre, double-blind, superiority RCT in the respiratory departments of 12 general hospitals in China. It is anticipated that 456 patients with AECOPD with a blood eosinophil count >2% or >300 cells/μL at admission will be recruited. Eligible patients will be randomised (1:1) to the intervention group receiving 40 mg oral prednisone daily or identical-appearing placebo (control group) for five consecutive days. Follow-up visits are performed during hospitalisation, followed by clinic interviews on days 30, 60 and 90 after discharge. The primary outcome is treatment failure rates comprising requiring or receiving invasive or non-invasive mechanical ventilation, requiring or transferring to intensive care unit during the index hospitalisation, length of index hospitalisation longer than 14 days, death during the index hospitalisation or within 30 days after discharge and readmission with acute exacerbations of COPD within 30 days after discharge. The results of this trial will provide insight into the value of using blood eosinophil counts as a biomarker of eosinophilic exacerbation and initiating systematic corticosteroid treatment for patients with AECOPD with higher eosinophil levels.

Ethics and dissemination This study was approved by Beijing Chaoyang Hospital Institutional Review Board (approval number: 2020-KE-544) and the main results and secondary results will be published in peer-reviewed journals.

Trial registration number NCT05059873.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a nationwide, multicentre, double-blind randomised controlled trial (RCT) in China.
⇒ The results of this RCT will help optimise the evidence base for eosinophil-guided corticosteroid therapy for inpatient acute exacerbations of chronic obstructive pulmonary disease management with the highest level of evidence possible.
⇒ The duration of infection and distribution on the geographical and time scale are unpredictable, as well as the number of patients recruited at each centre.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the top three causes of death worldwide, characterised by persistent airflow obstruction.[1 2] Acute exacerbation of COPD (AECOPD) is often associated with COPD progression and prognosis, repeated utilisation of healthcare services, impaired quality of life and increased mortality.[3–5] Hospitalisation expenditures for acute exacerbations account for a significant part of the cost of patients with COPD, imposing a substantial economic burden on individuals and society.[6]

For decades, systematic corticosteroids have been the cornerstone of treatment for patients with moderate and severe AECOPD resulting in reduced recovery time, improved lung function and reductions in the risk of relapse and treatment failure.[7] However, the use of systematic corticosteroids has potential side-effects, including increased risk of infections, osteoporosis, adrenal insufficiency, venous thromboembolism, hyperglycaemia, gastrointestinal bleeding, sepsis and heart failure, which can affect patients' prognoses.[8 9] In light of this, it is crucial to minimise the cumulative dose of corticosteroids while effectively treating exacerbations. In 2013, the Reduction in the Use of Corticosteroids in Exacerbated COPD (REDUCE) trial found that a short course of systematic corticosteroid treatment (40 mg prednisone for 5 days) was non-inferior to a 14-day treatment for patients with AECOPD when it came to re-exacerbation, length of stay (LOS) in the hospital, lung function and mortality.[10] In terms of treatment failure, re-exacerbation rates and mortality, oral treatment is not inferior to intravenous treatment.[11] As a result, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline recommends 5-day oral systematic corticosteroids for patients with AECOPD.[12] However, the use of systematic corticosteroids does not affect the long-term decline in lung function, the LOS in hospital intensive care units (ICUs), re-exacerbation of COPD after the first month or the mortality rates.[11] Therefore, the use of simple biomarker that identifying patients with particular AECOPD phenotypes, which will have a beneficial response to treatment with corticosteroids, has recently attracted much interest.

There is increasing evidence that blood eosinophil levels could be used as a biomarker to predict which patients will respond best to inhaled or systematic corticosteroids. A peripheral blood eosinophil count greater than 2% or 300 cells/μL is associated with an increased risk of AECOPD[13 14] and being more likely to benefit from treatment with inhaled and systematic corticosteroids.[15–18] In this way, this biomarker has been proposed as a biomarker to identify an eosinophilic COPD phenotype,[14 16] and guides the treatment of AECOPD with systematic corticosteroids.[15 19 20]

A small randomised controlled trial (RCT) of outpatient exacerbations demonstrated that oral corticosteroid was safe for patients with blood eosinophil counts >2%, whereas treatment in the low eosinophil group was associated with less improvement in chronic respiratory questionnaire scores and more treatment failures.[18] These findings suggest that patients with severe exacerbations of COPD and low blood eosinophil counts could be safely treated without systematic corticosteroids, reducing the risk of potential side-effects associated with this therapy. However, the study had a limited impact on current recommendations due to the limited sample size.

Moreover, theCORTICOsteroid reduction in COPD (CORTICO-COP) trial with large-scale sample sizes published in 2019 investigated an eosinophil-guided approach to corticosteroid treatment based on daily blood eosinophil counts. In the trial, patients with blood eosinophil levels ≥300 cells/μL received systematic corticosteroid treatment, while treatment was withheld on treatment days when blood eosinophil levels were below that threshold. The main finding was that the eosinophil-guided strategy was non-inferior to standard treatment (ST) for the number of days alive and out of hospital, and decreased the accumulated dose of systematic corticosteroids by approximately 60%.[5] The trial confirms that patients with severe AECOPD and low blood eosinophil counts can be safely treated without systematic corticosteroids, reducing the risk of potential side-effects associated with this therapy.

Taken together, there is one clarification that should be made—can standard systematic corticosteroid therapy benefit patients admitted with AECOPD with elevated eosinophil levels? There is a scarcity of evidence from relevant large sample double-blind placebo randomised controlled clinical trials. Therefore, our study aims to determine whether 5-day systematic corticosteroid compared with placebo could decrease the risk of treatment failures among hospitalised patients with AECOPD with blood eosinophil count >2% or 300 cells/μL.[13–15 19 21–23]

METHODS

Study design

This is an investigator-initiated, multicentre, randomised, double-blind, parallel controlled, superiority trial in the respiratory departments or the respiratory and critical care medicine departments at 12 general hospitals in Beijing. The details of the participating hospitals are listed in online supplemental appendix 1.

The study was prospectively registered with ClinicalTrials.gov on 10 August 2021. This protocol has been designed in accordance with the Standardised Protocol Items: Recommendations for Interventional Trials guidelines and checklist. The flow chart of this trial is shown in figure 1.

Patient and public involvement

Patients and the public were not involved in planning the design and conducting, reporting or disseminating the results of this study. And all of the results of this study will be published by the authors in relevant peer-reviewed journals regardless of the results.

Participant recruitment

A primary screening procedure consists of blood eosinophil tests conducted by study centres within 2 hours of admission. Eosinophil levels should be assessed as soon as possible after admission, especially in emergency rooms, before corticosteroids are administered. Patients who have received prednisone ≥60 mg in the past 3 days (or equivalent doses of other corticosteroid) will be excluded. Consecutive patients with AECOPD admitted

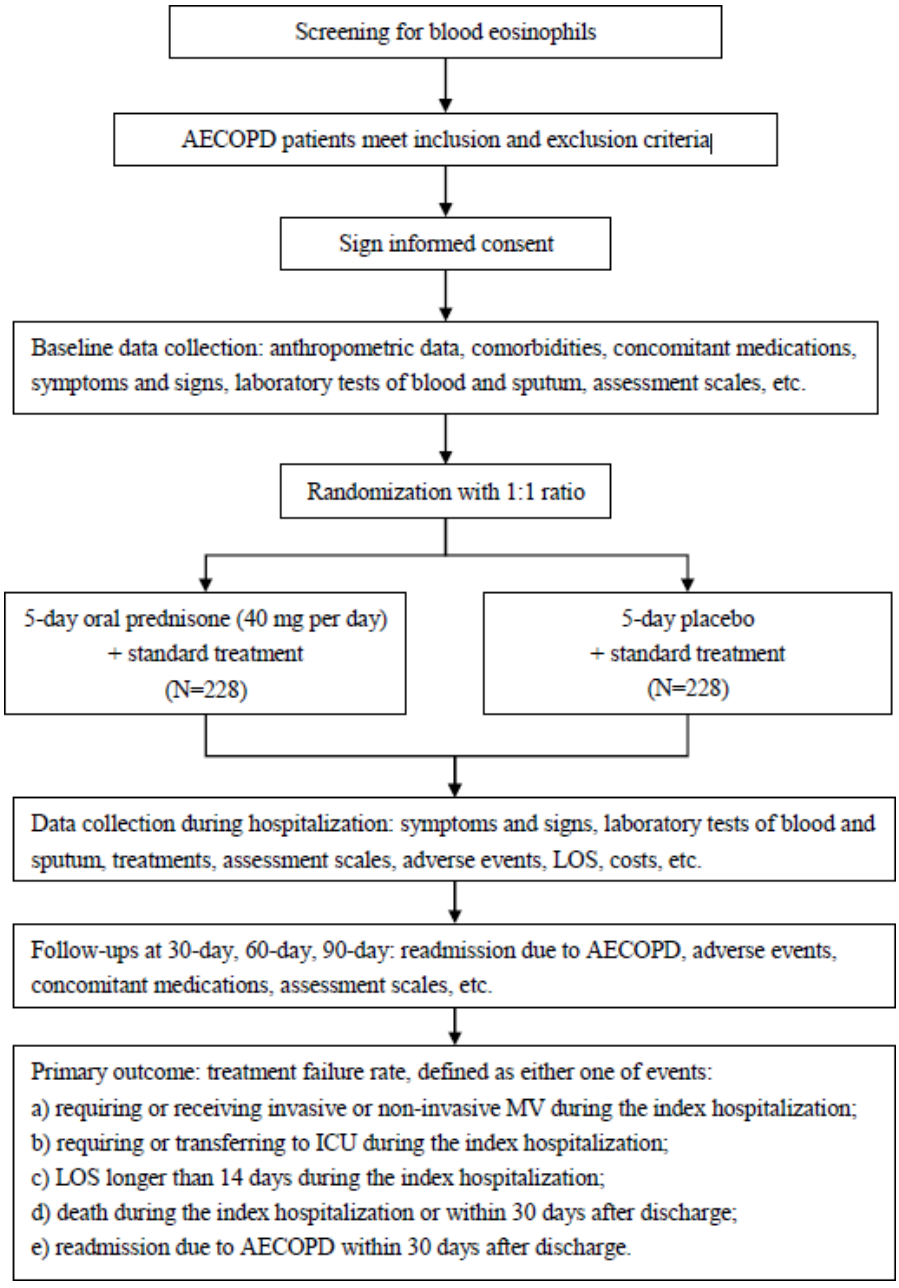

Figure 1 The flow chart of the ECHO trial. AECOPD, acute exacerbation of chronic obstructive pulmonary disease; ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation.

to participating centres will be invited by research physicians to participate in this trial if they meet the inclusion and exclusion criteria and sign an informed consent form. All of the inclusion and exclusion criteria are presented in table 1.

Randomisation

A web-based central randomisation system will be used for block randomisation (block size: four) stratified by participating hospitals. Eligible patients will be allocated to the systematic corticosteroid group or control group (receiving placebo group), with a ratio of 1:1. On entering the basic information, the randomisation system will automatically assign a random number. Once the random number has been assigned to a participant, the number cannot be reassigned. The randomisation sequence and concealment will be determined using the above-mentioned central randomisation system provided by Ericure (Beijing, China), which will not be involved in the recruitment of participants.

Blinding

Prednisone (5 mg) tablets and placebo have been produced and packaged in identical bottles with 100 tablets by Tianjin KingYork Pharmaceutical (Tianjin, China), in an environment regulated by Good Manufacturing Practice. The appearance of the placebo tablet is identical to the prednisone tablet. Each bottle is labelled with a computer-generated random alphanumeric code. The drugs will be administered to each enrolled

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Within 24 hours of admission. 2. Aged between 40 and 80 years old. 3. Established clinical history of COPD with spirometry-verified COPD (defined as post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) ≤0.70). 4. AECOPD diagnosis in accordance with the GOLD guideline.[21] 5. Current or former cigarette smokers (≥10 packs per year). 6. Blood eosinophil count >2% or >300 cells/μL tested within 24 hours of admission. 7. Signed informed consent.	1. Admission due to other diseases (pneumonia, pneumothorax, pulmonary interstitial disease, active tuberculosis or bronchiectasis, asthma and so on). 2. Regular use of glucocorticoid ≥3 months. 3. Received prednisone ≥60 mg in the past 3 days (or equivalent doses of other corticosteroids). 4. Allergic or intolerant to corticosteroid. 5. Participating in or completing another drug trial within 90 days. 6. Pregnancy or lactation. 7. Severe COPD exacerbation requiring invasive mechanical ventilation (IMV) or transfer to an intensive care unit (ICU) within 24 hours after emergency admission or hospitalisation. 8. With complications that may cause eosinophilia. 9. Pulmonary embolism within the past 2 years. 10. Myocardial infarction, uncontrollable congestive heart failure or arrhythmia within the past 4 weeks. 11. Comorbidities that may influence the immune system. 12. Malignant tumour. 13. Neuromuscular disease affecting the respiratory system. 14. Systematic fungal infection. 15. Thoracotomy or bronchoscopic lung volume reduction surgery history. 16. Adrenocortical insufficiency history. 17. Diabetes mellitus with poor glycaemic control. 18. Uncontrolled severe psychiatric illnesses even with medication, cognitive impairment and severe language difficulties. 19. Alanine aminotransferase (ALT) ≥100 U/L or aspartate transaminase (AST) ≥80 U/L. 20. Serum creatinine ≥162 μmol/L. 21. Life expectancy of less than 30 days.

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

participant in a bottle labelled with the corresponding code. Study participants, physicians, outcome assessors and data analysts will all be blinded to group allocation. Unblinding is permissible if necessary for the urgent medical treatment of a participant.

Study groups and interventions

Systematic corticosteroid group

Participants will receive oral prednisone 40 mg daily for five consecutive days in addition to ST during hospitalisation. Prednisone should be discontinued if severe adverse events (SAEs) occur, such as osteonecrosis of the femoral head, spontaneous fracture or haemorrhagic tendency and so on.

Control group

Participants will receive oral placebo 40 mg daily for five consecutive days in addition to ST during hospitalisation.

Standard treatment

During hospitalisation, all treatments will be administered in accordance with GOLD recommendations except for systematic corticosteroids,[21] including nonpharmacological treatments (nutritional support, oxygen therapy, non-invasive ventilator, sputum aspiration and so on) and pharmacological treatments (inhaled drug therapy such as short-acting muscarinic antagonists (SAMA), short-acting β_2-agonist (SABA), long-acting muscarinic antagonists (LAMA), theophylline, expectorants, antibiotics, nebulisation therapy including SABA and/or SAMA, or acetylcysteine and so on). However, nebulised corticosteroid therapy and inhaled corticosteroids (ICS) are required not to be used during emergency admission or hospitalisation.

After discharge, non-pharmacological treatments such as long-term oxygen therapy as well as pharmacological treatments including bronchodilators (SABA, SAMA, long-acting β2-agonist, LAMA), ICS and expectorants are allowed. During the entire study period, all participants are prohibited from using macrolides, since the GOLD 2023 demonstrated that azithromycin or erythromycin for 1 year in patients prone to exacerbations reduced the risk of exacerbations compared with usual care.[24 25] Therefore, we restricted the use of macrolides to minimise their possible confounding effect on outcome assessment. As well, the use of traditional Chinese medicine is prohibited to avoid potential confounding effects. The post-trial care in both groups will be the same and correspond to usual care.

Measurement and data collection

After confirmation of eligibility and completion of informed consent, a detailed assessment of the clinical symptoms and physical signs, ECG and assessment scales, including the Exacerbations of Chronic Pulmonary

Disease Tool (EXACT),[26] modified Medical Research Council (mMRC) Dyspnea Scale,[27] COPD Assessment Test (CAT),[28] Baseline Dyspnea Index[29] and Hospital Anxiety and Depression Scale (HADS)[30] are required before randomisation. The other baseline data are collected after randomisation within 24 hours of admission, including the participant's anthropometric information, risk factors for AECOPD, comorbidity, concomitant medications, the number of acute exacerbations in the past year, the pulmonary function (the last stable result within 6 months) and results from chest high-resolution CT, echocardiography and arterial blood gas analysis (online supplemental appendix 2). In addition, participant's pharmacotherapy for AECOPD, respiratory support therapy and condition changes (requiring or receiving MV, requiring or transferring to ICU, death) will be recorded after randomisation. During the 5-day intervention period, clinical symptoms, physical signs and laboratory tests of blood will be collected daily. The EXACT, mMRC and CAT will be assessed repeatedly on day 3 and day 6. Within 24 hours after discharge or the occurrence of in-hospital death, the LOS and medical cost of this hospitalisation will be collected. For those alive at discharge, clinical symptoms, physical signs and assessment scales will be accessed, and the results of blood and sputum will be obtained within 24 hours before discharge.

On discharge, participants will be followed up for 3 months. During this period, patients will be required to use the COPD Exacerbation Recognition Tool (CERT) for self-evaluation whenever symptoms of suspicious acute exacerbation emerge and to call their physicians. Three monthly face-to-face outpatient appointments will be used to assess their survival status, readmission due to AECOPD, infection, smoking status, concomitant medications, laboratory tests of blood, AEs and scores of assessment scales. The pulmonary function test will be conducted at 3-month follow-up. The schedule of measurements and visits for this trial is outlined in table 2. Once a patient is enrolled or randomised, the study site will make every reasonable effort to follow the patient throughout the entire study period, including helping them make medical appointments and providing them with traffic allowances.

Data management

A web-based data management system (DMS) will be used to facilitate data collection and central management during the entire trial. Data will be subjected to a full set of web-based DMS validation checks and additional manual data-checking procedures to assure the quality of data entry. Only authorised personnel are permitted access to stored information. The principal investigator will have access to the full data set, and co-investigators and the steering committee will have access as needed for random auditing. Identifiable participant information is stored on paper forms in locked filing cabinets within a restricted area of each site. All trial documentation and data will be archived for at least 5 years following completion of the trial.

Outcomes

The primary efficacy outcome is treatment failure rates. Treatment failure is defined as either one of these events: (a) requiring or receiving invasive or non-invasive MV during the index hospitalisation; (b) requiring or transferring to ICU during the index hospitalisation; (c) length of index hospitalisation longer than 14 days; (d) death during the index hospitalisation or within 30 days after discharge and (e) readmission with acute exacerbations of COPD within 30 days after discharge.

Secondary outcomes, in addition to the individual components of treatment failure above, include all-cause mortality within 90 days after discharge, readmission rates of AECOPD at 60-day and 90-day follow-ups, time to readmission of AECOPD within 90 days after discharge, severe infection or development of pneumonia during hospitalisation, length of hospital stay during hospitalisation and changes in assessment scales (EXACT, mMRC, CAT, TDI, HADS, SGRQ, CERT) during hospitalisation and within 90 days after discharge. The details of time frames of each assessment scale are listed in table 2.

Sample size

The aim of this trial was to establish whether oral systematic corticosteroid therapy was superior to placebo in terms of clinical outcome (treatment failure rates). Based on a Cochrane meta-analysis on administration of systematic corticosteroids compared with placebo,[11] the treatment failure rate of the corticosteroid treatment group was approximately 50% lower than that of the placebo control group. The failure rate of the intervention group and control group is assumed to be 13% and 25%, respectively. A margin of superiority of 12% is considered to be a minimally clinically relevant difference in patients with AECOPD.[11] There will be 205 patients in each group, 410 in total, in order to have 80% power, assuming that the type I error rate is 5%. The final study population is comprised of 456 patients assuming a dropout rate of 10%.

Statistical analysis

The primary analyses will follow the intention-to-treat principle. The differences in baseline variables between groups will be evaluated by using a t-test, Wilcoxon rank test or χ^2 test. Logistic regression will be used to compare the odds of treatment failure between two groups after adjusting for sites (hospitals). If more than 5% of patients are lost to follow-up, multiple imputations by chained equations will be performed. The variables used to impute the missing values of the primary outcome will include participants' available values of each composite outcome, as well as other variables that are associated with this outcome (such as age, number of AEs in the past year). Sensitivity analyses will be conducted in order to adjust for imbalanced baseline variables if they exist

Table 2 The schedule of measurements and visits of this trial

	Study period							
	Baseline	Treatment period						Follow-up period
	Admission within 24 hours	Day 2	Day 3	Day 4	Day 5	Day 6	At discharge	1, 2, 3 months
Eligibility screen	×							
Anthropometric data	×							
Risk factors	×							×
Comorbidity	×							
Concomitant medications	×							×
The history of acute exacerbations	×							
Clinical symptoms	×	×	×	×	×	×	×	
Physical signs	×	×	×	×	×	×	×	×
Laboratory tests of blood	×	×	×	×	×	×	×	×
Laboratory tests of sputum	×				×		×	
Pulmonary function	×							×*
EXACT	×		×			×	×	×
mMRC & CAT	×					×	×	×
BDI	×							
TDI			×			×	×	×
HADS	×						×	×
SGRQ							×	×
CERT								×†
Pharmacotherapy for AECOPD	×	×	×	×	×	×		
Respiratory support therapy	×	×	×	×	×	×		
Study outcomes							×	×
Adverse events	×	×	×	×	×	×	×	×

*Only on 3 month.
†Everyday.
AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BDI, Baseline Dyspnea Index; CAT, COPD Assessment Test; CERT, COPD Exacerbation Recognition Tool; EXACT, exacerbations of chronic pulmonary disease tool; HADS, Hospital Anxiety and Depression Scale; mMRC, modified Medical Research Council Dyspnea Scale; SGRQ, St. George's Respiratory Questionnaire; TDI, Transition Dyspnea Index.

and to repeat the analyses with imputed missing values due to lost follow-ups. As part of the secondary analysis, per-protocol analyses will be conducted on participants who have received the full trial interventions and have completed assessment of the primary outcome. The details of patients who will be excluded from per-protocol analyses are listed in online supplemental appendix 3. Subgroup analyses will be performed to identify potential modifiers of the intervention effect, including gender, age, baseline blood eosinophil count, respiratory failure at admission or not, the number of hospitalisations and number of emergency admissions for AEs in the prior year. There will be no interim analyses. A statistically significant p value is less than 0.05.

AE reporting

AEs during the whole study period will be recorded in the case report form (CRF). The pre-defined intervention-related AEs are listed in online supplemental appendix 4. AEs are required to be reported within 24 hours to the principal investigator. The data safety monitoring board consisting of a pulmonologist, respiratory nurse and clinical epidemiologist surveys the study and evaluates SAEs. Commercial insurance (Taiping General Insurance) will be provided for all participants to cover non-negligent harm associated with the protocol. This will include cover for additional healthcare, compensation or damages whether awarded voluntarily by the Sponsor, or by claims pursued through the courts.

Ethical and dissemination

This study adheres to the Declaration of Helsinki and guidelines for Good Clinical Practice. Each participant will sign an informed consent form. Participant data in the DMS will be protected by password and only be accessible to users with appropriate authorisation levels designated

by the study. De-identified data will be used for statistical analysis. The principal investigator of the ECHO study (ZT) will be given access to the cleaned full data sets. The principal investigators of each site will have direct access to their own site's data sets and will have access to others' sites' data on request. The current trial has been approved by the Beijing Chaoyang Hospital Institutional Review Board (approval number: 2020-KE-544) and registered on ClinicalTrials. gov. The results of this trial will be disseminated through academic conferences and publications in international peer-reviewed journals.

Quality control

The quality control team was assembled before the initiation of this study. Each researcher participating in this study must attend the technical training and pass the examination organised by the coordinating centre, including the study protocol, informed consent, CRF and standard operating procedures for collecting patients' data. Each site will be audited on-site by independent clinical research associates (CRAs) following its kick-off meeting, after recruiting the first three patients, after the completion of the last patient, and if necessary, during causal and collaborative auditing. CRAs will verify all predefined key study variables for all enrolled participants and a random sample of 10% of included participants. If necessary, the quality control team will convene a teleconference with the executive committee. Any modifications to the protocol that may impact the conduct of the study, potential benefit of the patient or may affect patient safety, including changes in study objectives, study design, patient population, sample sizes, study procedures or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed on by the executive committee of ECHO study and approved by the institutional review board prior to implementation.

DISCUSSION

Recent research has highlighted the heterogeneity of the pathological characteristics of COPD, leading to a growing interest in personalisation of care for patients. Blood eosinophils are a potential biomarker for phenotyping patients with COPD who will benefit from corticosteroid treatment. On the basis of post-hoc studies of RCTs, it has been recommended that the use of blood eosinophil levels guides ICS therapy in patients with stable COPD to prevent patients from being exposed to unnecessary ICS.[5 31]

In the case of AECOPD, limited evidence from RCTs demonstrates that blood eosinophil levels can be used to guide decreasing exposure to systematic corticosteroid treatment. However, these studies have had little impact on the guidelines, in part because of methodological limitations that need to be addressed. Bafadhel *et al*,[17 18] for example, conducted an RCT with a small sample size (n=164) focusing on AECOPD outpatients, only 10 patients were admitted to the hospital due to exacerbations. Therefore, these findings cannot be extrapolated to severe acute exacerbations, particularly those requiring hospitalisation or emergency admission. In addition, a meta-analysis of three clinical trials (n=243) demonstrated the effectiveness of using blood eosinophil-guided systematic corticosteroids to treat AECOPD, compared with placebo.[17] However, a note of caution is due here since the analysis involved more patients with blood eosinophil counts of <2% at exacerbation receiving antibiotic therapy in the prednisone group compared with the non-prednisone group. Consequently, these results are inconclusive or indeterminate. Furthermore, the CORTICO-COP trial published in 2019 focused on using blood eosinophil counts (>300 cells/µL) to reduce the overall systematic corticosteroid exposure during hospitalisation.[5] However, the open-label design of the trial might have led to bias in assessing outcomes. This could have been partly mitigated by including a placebo group.

Different from abovementioned studies, our ECHO study was designed to recruit AECOPD inpatients with an eosinophilic COPD phenotype defined as blood eosinophil counts of >2% or >300 cells/µL. An important strength of this study relates to its prospective, randomised, placebo-controlled and double-blind design as well as its relatively large sample size, with 456 participants anticipated to be enrolled. In addition, we have a set of outcome measurements, which are selected according to the European Respiratory Society recommendation[32] to reflect the efficiency, safety and health economics of our eosinophil-guided corticosteroid therapy for inpatient AECOPD management. The primary outcome in our study, treatment failure rate, which comprises deterioration during hospitalisation, prolonged LOS, all-cause mortality and readmission with AECOPD within 30 days after discharge, is most commonly used in recent relevant studies[32] and recommended more than other outcomes.[33] Thus, we consider the outcome measurements in the ECHO study to be optimal as well as comparable to other relevant studies.

Despite this, the major limitation of this study is its use of a single blood eosinophilic measurement taken within 24 hours of admission for identification of patients with elevated levels of eosinophils. To minimise misclassification bias, we will exclude patients who have received systematic corticosteroids prior to hospitalisation. Given that blood eosinophil levels can fluctuate widely in individual patients and decrease rapidly following corticosteroids administration, serial measurements of blood eosinophils may be more reliable.[17] However, it is clinically infeasible to measure peripheral blood eosinophils a few times before deciding whether systematic corticosteroid therapy should be administered. In such cases, patients may miss the ideal time to start corticosteroids.

In addition, in our ECHO study, the threshold for blood eosinophil counts is 2% or 300 cells/µL,[5] but its optimal limit remains uncertain. Numerous retrospective studies investigated the optimal cut-off value of blood eosinophil

count to identify patients with AECOPD who might benefit from systematic corticosteroids, ranging from 150 cells/μL to 500 cells/μL or from 2% to 5%.[5 15 19 34–38] One of the most common thresholds for increased blood eosinophilia in several RCTs of eosinophil-guided systematic corticosteroid therapy was 2% or 300 cells/μL.[5 18 38] Therefore, the threshold for our ECHO study was set at >2% or >300 cells/μL to ensure that as many patients as possible with increased blood eosinophilia would be considered for administration of systematic corticosteroids.

In all, the ECHO study will provide a unique opportunity to better understand the clinical significance of using blood eosinophil counts of >2% or >300 cells/μL measured at admission for identifying inpatients with AECOPD who can benefit from oral systematic corticosteroid treatment and reduce the risk of AEs as a result of inappropriate exposures while hospitalised. By the end of our study, we will present evidence that will facilitate the eosinophil-guided precision approach to a problem characterised by one-size-fits-all solutions.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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