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Blood Eosinophils in Chinese COPD Participants and Response to Treatment with Combination Low-Dose Theophylline and Prednisone: A Post-Hoc Analysis of the TASCS Trial

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Background and Objectives: The burden of chronic obstructive pulmonary disease (COPD) disproportionately affects patients in low to middle-income countries. Although the Theophylline and Steroids in COPD Study (TASCS) showed no clinical benefit from administering low-dose theophylline and prednisone in COPD patients compared to placebo, it was hypothesized that those with elevated blood eosinophil counts would receive clinical benefit from the intervention.

Methods: This was a post-hoc analysis of the TASCS dataset – a double-blinded, placebo-controlled trial conducted in patients with moderate–severe COPD in China. Participants were allocated 1:1:1 to low-dose oral theophylline (100mg bd) and prednisone (5mg qd; PrT), theophylline (100mg bd) and prednisone-matched placebo (TP), or double-matched placebo (DP) groups and followed-up for 48 weeks. A baseline count of ≥300 eosinophils/μL blood was categorized as elevated/eosinophilic, and the primary outcome was the annualized moderate-severe exacerbation rate.

Results: Of 1487 participants eligible for analysis, 325 (22%) were eosinophilic. These participants were predominantly male (82%), had a mean (SD) age of 64 (±8) years and a predicted forced expiratory volume in 1s (FEV_1) of 43% (±16). The annualized moderate–severe exacerbation rate was significantly higher in the PrT group compared to the pooled results of the TP and DP groups (incidence rate ratio = 1.6; ([95% CI 1.06–1.76]) p = 0.016). Changes in spirometry values and reported disease impact scores (St. George's Respiratory Questionnaire and COPD Assessment Test) at week 48 were not significantly different between groups.

Conclusion: Combination low-dose theophylline and prednisone was associated with a significant increase in the annual moderate-severe exacerbation rate in participants with a blood eosinophil count ≥300 cells/μL compared to placebo.

Keywords: eosinophil, COPD, clinical trial, China, theophylline, prednisone

Introduction

Chronic obstructive pulmonary disease (COPD) continues to be a major cause of morbidity and mortality worldwide, with an estimated prevalence of approximately 3% of the global community in 2019.[1] Current guidelines recommend use of long-acting bronchodilators to reduce symptoms and exacerbations, with the addition of inhaled corticosteroids when exacerbations become more frequent, particularly if blood eosinophil counts are raised above 300 cells/μL.[2] For

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significant portions of the global patient population, these pharmacotherapies are often under-utilized due to limited access and affordability – necessitating the use of low-cost alternatives where available.

Previous in vitro and in vivo studies had suggested that the activity of histone deacetylase-2 (HDAC2), a nuclear enzyme that inhibits inflammatory gene expression, is markedly reduced in COPD. By interfering with the anti-inflammatory effects of corticosteroids, HDAC2 can be increased by low concentrations of theophylline, restoring corticosteroid responsiveness.[3–6] Thus, it was hypothesized that theophylline could promote anti-inflammatory gene expression and restore sensitivity to glucocorticosteroids in COPD patients, hence improving their response to prednisone. In the absence of access to gold standard bronchodilator therapy, this pharmacologic synergism could potentially provide an affordable and highly accessible management strategy for COPD patients in resource-poor settings.

The "Theophylline And Steroids in COPD Study" (TASCS) was a multicenter randomized control trial undertaken in China to determine if the effect observed in vitro translated into clinical benefit in a large randomized controlled trial. Neither TASCS, nor the "*Theophylline With Inhaled Corticosteroids*" (TWICS) trial observed a significant treatment effect with the addition of low doses of theophylline with regards to exacerbation rate or risk, lung function or disease-related quality of life and symptom impact questionnaire scores.[7,8]

However, the pathological heterogeneity of COPD opens the possibility for further investigation of patient subpopulations in whom beneficial effects might occur. Post-hoc analyses of data from randomized controlled trials for COPD pharmacotherapy have previously demonstrated that an elevated blood eosinophil count is associated with an enhanced response to inhaled corticosteroids (ICS).[9–15] We performed this post-hoc analysis to determine if a novel maintenance therapy of combination low-dose theophylline and an oral corticosteroid was associated with a reduction in exacerbation frequency in participants with COPD and elevated blood eosinophil counts.

Methods

TASCS has been reported previously.[8] Briefly, TASCS (NCT02261727) was a 48-week, multicenter, double-blinded, randomized, parallel study conducted at urban and regional hospitals around China. Study protocol and informed consent procedures were centrally approved by The University of Sydney Human Research Ethics Committee (protocol no. 2012/082) and the institutional review board at each site. All patients provided written informed consent prior to undertaking any study-specific procedures. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice.

The primary objective was to determine if a combination of oral prednisone 5mg qd and low-dose theophylline 100mg bd (PrT) was superior to placebo in reducing the annualized rate of acute exacerbations of COPD (AECOPD) at 48 weeks compared to the pooled results (herein referred to as Pooled Placebo; PP) of the double-placebo and low-dose theophylline 100mg and placebo study groups.

Other secondary objectives included change in St. George Respiratory Questionnaire (SGRQ) score, COPD Assessment Test (CAT) score, post-bronchodilator spirometry, safety, and time to first acute exacerbation of COPD.

Participants

Consented and eligible participants were aged 40 to 80 years with a clinical diagnosis of COPD and were current or former smokers with at least 10 pack years or 10 years exposure to other sources of combusted biomass. At screening and baseline, participants had a post-bronchodilator FEV_1 <70% predicted and an FEV_1/FVC ratio <0.7, and in the prior 12 months had experienced at least one AECOPD that was treated with systemic corticosteroids and/or antibiotics or had led to hospitalization. A full list of inclusion and exclusion criteria can be found in the primary publication.[8] Participants were included in this analysis if they had blood eosinophil counts recorded at the screening visit, had been randomized to a treatment group, and had been in follow-up for at least 2 weeks before trial discontinuation.

Endpoints and Assessments

The primary efficacy endpoint was the annualized moderate-severe AECOPD rate. These events were identified when the participant experienced a worsening in health for at least two consecutive days with two or more major symptoms (dyspnea, sputum volume increase, sputum purulence) or a worsening of one major symptom with any one minor

symptom (sore throat, nasal discharge, nasal congestion, fever without other cause, cough or wheeze). Severity of the event was graded as (I) mild if addressed with any form of symptomatic treatment, (II) moderate if managed with systemic corticosteroids and/or antibiotics and (III) severe if it resulted in emergency department presentation or hospitalization. Secondary endpoints were the overall and severity-stratified AECOPD rates, time to first AECOPD, the change in FEV_1 and the SGRQ and CAT questionnaire scores at 48 weeks. Adherence to intervention was reported as ≥80% (high), ≥60% to <80% (moderate) and <60% (low).

Statistical Methods

The primary analysis group was defined by an absolute count of ≥300 eosinophils/μL of blood (referred to as ≥300). Secondary exploratory groupings were defined by a cut-off of ≥150 eosinophils/μL and ≥3% of total white blood cell (WBC) count.

All comparisons were made between the PrT and PP groups unless specified otherwise. Statistical significance was defined as $p < 0.05$. Difference in AECOPD count between treatment groups was assessed with a hierarchical negative binomial regression model (with recruiting site as random effect) adjusted for a pre-defined fixed-effects covariates set including age, sex, region, baseline percentage predicted post-bronchodilator FEV_1, baseline FEV_1 reversibility (% improvement in FEV_1 after nebulized short-acting β_2-agonist) and smoking status. Analysis was repeated with fixed effects only to obtain the adjusted, annualized AECOPD rates. In both models, the offset was the natural log follow-up time of each participant.

Secondary endpoints were lung function values obtained by spirometry, CAT and SGRQ, which were analyzed using multilevel mixed-effects linear regression with the similar fixed effects covariates as the primary outcome model. Cox Proportional Hazards Regression was used to assess risk of exacerbation. Univariable predictors of eosinophilia were also tested for using linear regression, ordinal or binomial logistic regression where appropriate. All analyses were conducted using Stata 16.1 (StataCorp LLC. 2019. Stata Statistical Software: Release 16.1. College Station, TX, USA).

Results

Participant enrolment commenced in June 2014 and the final patient completed the study in May 2018. Of the original 1670 randomized participants in the TASCS trial, 1487 participants had absolute blood eosinophil counts recorded at baseline, were randomized to a treatment group and remained in the study for 2 or more weeks. The median blood eosinophil count for this sample was 150 cells/μL (Interquartile limits (IQL) 8–26), with values of 15 cells/μL (IQL 8–27) and 160 cells/μL (IQL 80–260) for the PP and PrT groups, respectively.

At baseline, 325 (22%) of the included participants had blood eosinophil counts exceeding ≥300 cells/μL (Table 1). Within this participant group, the treatment allocation was proportionate to the full sample (PrT: n = 101, PP: n = 224) and the disposition of participants was similar. A total of 776 (52%) participants had counts exceeding ≥150 eosinophils/μL, and 571 (38%) had blood eosinophil percentages ≥3%.

Baseline Eosinophils and Exacerbation Rate by Treatment Group

At trial completion 51 of the 325 participants with a baseline blood eosinophil count ≥300 cells/μL had withdrawn from the study (34 [15%] in the PP group; 17 [17%] in the PrT group; Figure S1). Of the 325 subgroup participants, 160 (49%) of the participants with a baseline blood eosinophil count ≥300 cells/μL had experienced one or more AECOPDs. The PrT treatment group had 58 participants report 117 events, whilst the PP group had 102 participants reporting 187 events.

The PrT participants had significantly higher annualized moderate, severe, moderate-severe and overall AECOPD rates compared to their counterparts in the PP group (Figure 1). When the analysis was repeated without "site" as a random effect, it was found that only the moderate-severe AECOPD rate remained significantly different between the PrT and PP ($p = 0.037$) groups (Figure 2).

Alternative definitions of eosinophilia in COPD participants were also explored. At ≥150 cells/μL and ≥3% no significant difference in the moderate-severe AECOPD rate was observed between the treatment groups (Figures S2 and S3). This was also the case when absolute blood eosinophil count and eosinophils as a percentage of total WBCs were analyzed as continuous variables. Within the PrT arm of the study, participants with a baseline blood eosinophil count

Table 1 Demographics of Participants in the TASCS Sample at Baseline Who Had Blood Eosinophil Counts Recorded, Stratified by Eosinophilic Status (≥300 Cells/μL) and Treatment Group

	Eosinophilic Patients (≥300 Cells/μL)			Non-Eosinophilic Patients (<300 Cells/μL)			All Patients
	Placebo (n=224)	Drug (n=101)	Total (n=325)	Placebo (n=769)	Drug (n=393)	Total (n=1162)	(n=1487)
Age, yrs (sd)	63.79 (8.03)	64.87 (6.81)	64.13 (7.68)	64.51 (7.96)	65.17 (7.17)	64.73 (7.85)	64.6 (7.82)
Sex, male (%)	185 (82.59)	81 (80.2)	266 (81.8)	585 (76.07)	286 (72.77)	871 (75.0)	1137 (76.46)
BMI (sd)	23.03 (3.47)	22.25 (3.71)	22.78 (3.56)	22.14 (3.45)	22.36 (3.45)	22.21 (3.45)	22.34 (3.48)
Regional Location, n(sd)	93 (41.52)	46 (45.54)	139 (42.8)	338 (43.95)	172 (43.77)	510 (43.9)	649 (43.64)
Smoking Status (%)							
Never	51 (22.77)	27 (26.73)	78 (24.0)	204 (26.53)	111 (28.24)	315 (27.1)	393 (26.43)
Past	131 (58.48)	56 (55.45)	187 (57.7)	418 (54.36)	201 (51.15)	619 (53.3)	806 (54.2)
Current	42 (18.75)	18 (17.82)	60 (18.5)	147 (19.12)	81 (20.61)	228 (19.6)	288 (19.37)
Mean Current PY (sd)	43.06 (19.13)	49.95 (19.05)	45.35 (19.63)	43.45 (26.51)	45.06 (22.98)	44.03 (25.28)	44.3 (24.18)
Mean Past PY (sd)	40.17 (20.22)	37.38 (17.3)	39.33 (19.38)	39.67 (21.94)	36.75 (19.33)	38.72 (21.16)	38.86 (20.75)
Biomass Exposure, n(%)	73 (32.59)	37 (36.63)	110 (33.8)	293 (38.15)	162 (41.22)	455 (39.2)	565 (38.02)
Dust Exposure, n(%)	44 (19.64)	21 (20.79)	65 (20.0)	132 (17.17)	63 (16.03)	195 (16.8)	260 (17.48)
Spirometry							
FEV_1 Post, L (sd)	1.14 (0.44)	0.98 (0.41)	1.10 (0.43)	1.03 (0.41)	1.02 (0.42)	1.02 (0.41)	1.04 (0.42)
%FEV_1 Reversal (sd)	11.41 (13.62)	10.59 (18.70)	11.51 (15.62)	9.61 (15.37)	10.08 (12.8)	9.77 (14.45)	10.15 (14.8)
FEV_1 %predicted	43.95 (14.56)	40.8 (18.12)	42.97 (15.78)	41.43 (15.11)	41.36 (14.56)	41.41 (14.91)	41.75 (15.12)
FEV_1/FVC	44.43 (11.01)	44.49 (12.05)	44.45 (11.33)	45.51 (10.76)	44.96 (11.34)	45.32 (10.96)	45.13 (14.80)
GOLD Category n(%)							
1	1 (0.45)	0 (0.00)	1 (0.3)	8 (1.05)	3 (0.77)	11 (1.0)	12 (0.81)
2	68 (30.36)	21 (20.79)	89 (27.4)	186 (24.38)	96 (24.49)	282 (24.4)	371 (25.07)
3	114 (50.89)	51 (50.50)	165 (50.8)	381 (49.93)	202 (51.53)	583 (50.5)	748 (50.54)
4	41 (18.3)	29 (28.71)	70 (21.5)	188 (24.64)	91 (23.21)	279 (24.2)	349 (23.58)
SGRQ, score (sd)	45.82 (20.04)	46.73 (20.03)	46.1 (20.01)	45.99 (20.01)	46.01 (19.56)	46.00 (19.85)	46.02 (19.88)
CAT, score (sd)	18.23 (7.24)	18.35 (7.24)	18.27 (7.23)	18.16 (7.38)	17.97 (7.33)	18.1 (7.36)	18.13 (7.33)
Past year exacerbation [a], n(%)	106 (47.32)	53 (52.48)	159 (48.9)	360 (46.88)	182 (46.43)	542 (46.7)	701 (47.21)
Past year exacerbation rate [a] (sd)	0.68 (0.94)	0.83 (1.53)	0.72 (1.14)	0.69 (1.06)	0.64 (0.97)	0.67 (1.03)	0.68 (1.05)

Note: [a]Events in the 12 months prior to screening requiring oral corticosteroids, antibiotics or both.
Abbreviations:BMI, body mass index; FEV_1, forced expiratory volume – 1 second; FVC, forced vital capacity; CAT, COPD Assessment Test; SGRQ, St George Respiratory Questionnaire.

≥300 cells/μL the moderate-severe AECOPD rate was significantly higher than those with a cell count <300/μL of blood (Table S2A). The differences between these subgroups within the pooled placebo group were not significant (Table S2B).

Treatment allocation did not determine risk of experiencing an AECOPD of any severity, nor for the moderate-severe endpoint (Figures 3 and S4). The median time to first moderate-severe AECOPD for the PrT and PP groups within the ≥300 cells/μL group was 148.0 (IQR 98–278) and 200 (IQR 84–232) days, respectively. Similarly, no significant differences in AECOPD risk were observed in the ≥150 cells/μL and ≥3% groups between treatments (Figures S5 and S6).

Secondary Endpoints

Change in post-bronchodilator spirometry values from baseline to study completion was similar for treatment allocation groups. Within the ≥300 cells/μL participant group the difference in the adjusted mean decline of FEV_1 at 48 weeks was 18mL [95% CI −70 – 28] in the PP group and 7mL [−0.8–5] in the PrT group (P = 0.75). Similarly, no significant difference was observed between treatment groups for change in percent predicted FEV_1, change in absolute and percent predicted FVC, and the change in FEV_1/FVC ratio (Table 2).

At study completion, the changes from baseline CAT score, SGRQ total score (and sub-domains) were not significantly different between PrT and PP.

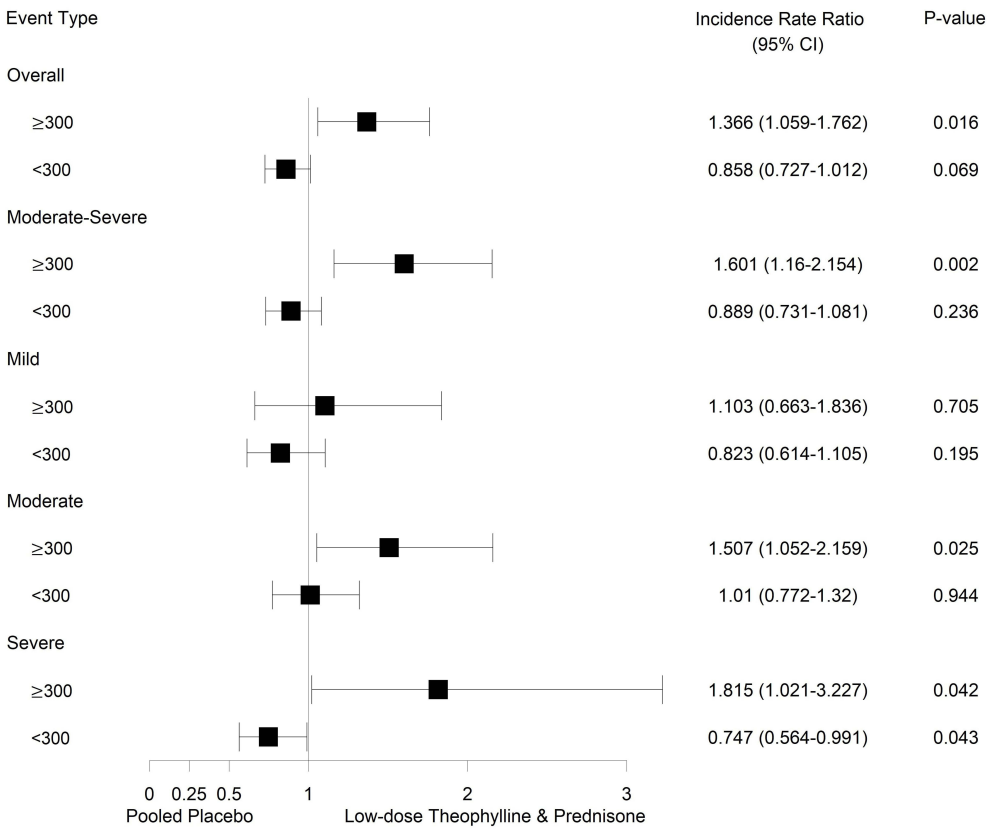

Figure 1 Forest plot describing the incidence rate ratios (95% CI) of acute exacerbations of chronic obstructive pulmonary disease between prednisone & theophylline and pooled placebo treatment arms in participants with blood eosinophil counts of <300 and ≥300 cells/μL, derived from a multi-level mixed effects model.

Analyses repeated with participants in the ≥150 and ≥3% groups demonstrated similar non-significance between changes in these secondary outcomes between treatment arms (Table S1).

Participant Disposition

Treatment group allocation did not predict premature study discontinuation, neither in the three eosinophil groups; ≥300 (OR 0.88 [0.47–1.67], p = 0.71), ≥150 (OR 1.13 [0.75–1.70], p = 0.554) and ≥3% (OR 0.94 [0.59–1.47], p = 0.788).

Intervention adherence was likewise not associated with eosinophil count at baseline or by inclusion in the ≥300 (OR 1.3 [0.84–2.02], p = 0.247) or ≥3% (OR 1.26 [0.85–1.76], p = 0.083) groups. However, membership in the ≥150 blood eosinophil group was associated with a higher level of adherence (OR 1.51 [1.06–2.14], p = 0.022).

Predictors of Eosinophilia

At baseline, the strongest univariate predictors of an eosinophil count ≥300 cells/μL were increased total WBC, monocyte, lymphocyte and neutrophil counts, as well as male sex, having a higher predicted post-bronchodilator FVC, higher absolute post-bronchodilator FEV_1, higher BMI, and a lower respiration rate (Table 3). Unit increases in blood eosinophil count occurred in parallel to increases in monocytes, lymphocytes, neutrophils, FVC (absolute and % predicted) and absolute FEV_1. Both analyses also showed elevations of blood eosinophils predicted by male sex and a higher absolute FEV_1 reversibility (Table S3).

Discussion

This study demonstrated that in Chinese participants with "Global Initiative for Chronic Obstructive Lung Disease (GOLD)" grade II–IV COPD and blood eosinophilia (≥300 cells/μL), who were randomized to receive low-dose oral theophylline with prednisone, experienced a significant increase in moderate-severe AECOPDs compared to the

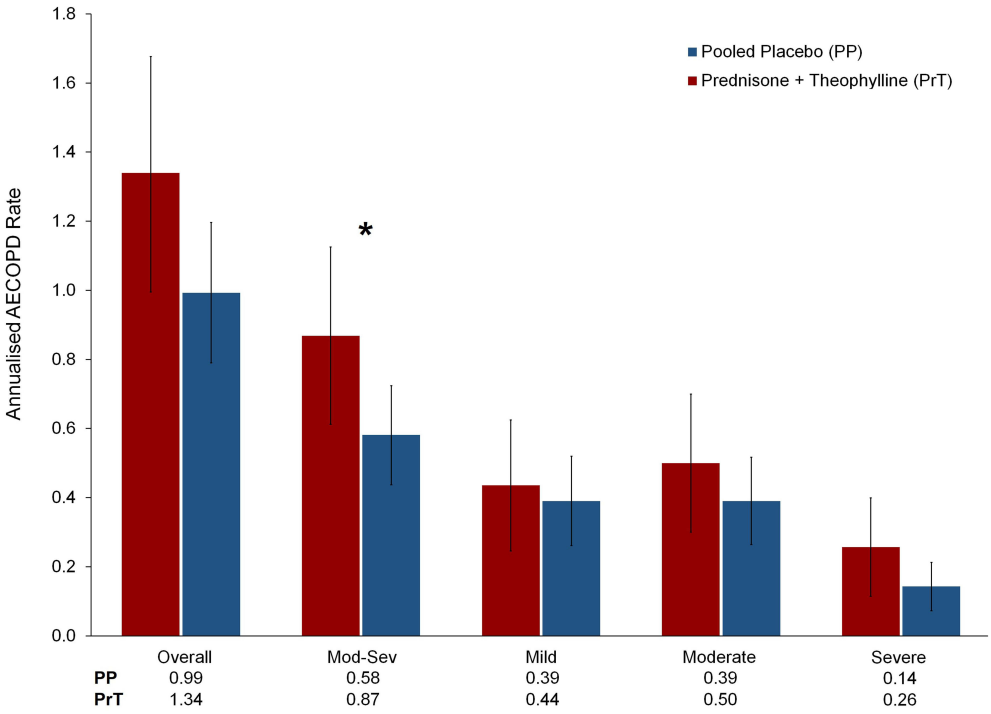

Figure 2 Adjusted annualised rates of acute exacerbations of chronic obstructive pulmonary disease (AECOPD) between prednisone & theophylline (PrT) and pooled placebo (PP) in participants with blood eosinophil counts ≥300 cells/μL derived from a fixed effects model. *p <0.05.

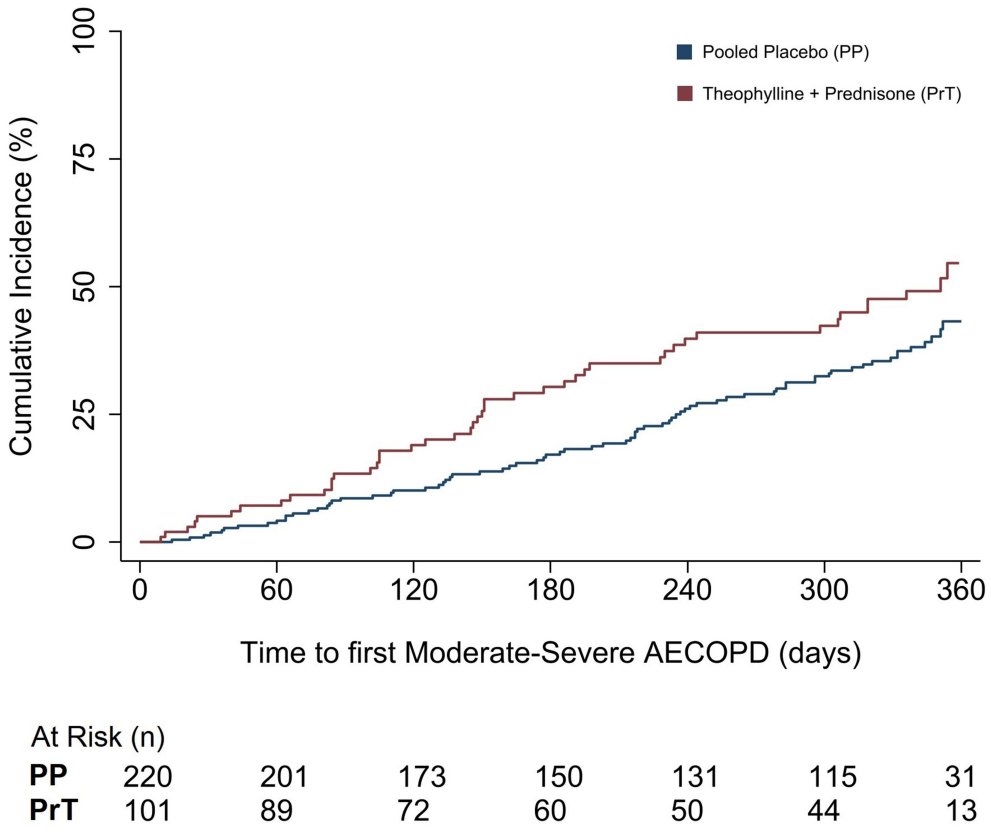

Figure 3 Kaplan-Meier plot of time to first moderate–severe acute exacerbations of chronic obstructive pulmonary disease (AECOPD) in participants with blood eosinophil counts ≥300 cells/μL in the prednisone & theophylline and pooled placebo treatment groups.

Table 2 Secondary Outcomes (Means, 95% CI) at Study Completion by Treatment Groups (Pooled Placebo and Prednisone & Theophylline) in Participants with Blood Eosinophil Counts ≥300 Cells/μL

	Pooled Placebo	Prednisone + Theophylline	Regression Coefficient	P-value
CAT Score Change	-3.82 (-5.37 – -2.27)[a]	-2.63 (-4.39 – -0.87)	1.19 (-0.29 – 2.68)	0.116
SGRQ Score Change				
Total	-8.02 (-12.48 – -3.56)	-9.52 (-14.59 – -4.45)	-1.50 (-5.91 – 2.91)	0.506
Symptom	-8.66 (-13.13 – -4.17)	-4.50 (-9.90 – 0.90)	4.15 (-0.96 – 9.26)	0.112
Activity	-5.74 (-10.01 – -1.48)	-5.56 (-10.50 – -0.61)	0.18 (-4.11 – 4.47)	0.933
Impact	-5.88 (-11.13 – -0.63)	-5.55 (-11.47 – -0.37)	0.33 (-4.32 – 4.99)	0.889
Spirometry Change				
FEV_1 (L)	-0.018 (-0.07 – 0.03)	-0.01 (-0.07 – 0.05)	0.01 (-0.06 – 0.08)	0.750
Predicted FEV_1 (% Point)	-0.56 (-2.66 – 1.54)	-1.38 (-4.04 – 1.27)	-0.82 (-3.63 – 1.99)	0.566
FVC (L)	-0.04 (-0.12 – 0.05)	0.02 (-0.09 – 0.13)	0.05 (-0.07 – 0.18)	0.407
Predicted FVC (% Point)	-0.49 (-3.42 – 2.44)	0.90 (-2.84 – 4.65)	1.40 (-2.64 – 5.43)	0.498
FEV1/FVC (%)	0.45 (-1.76 – 2.65)	-0.88 (-3.43 – 1.68)	-1.32 (-3.56 – 0.92)	0.248

Abbreviations: CAT, COPD Assessment Test; SGRQ, St George Respiratory Questionnaire; FEV1, forced expiratory volume – 1 second; % point, percentage-point change; FVC, forced vital capacity.

Table 3 Baseline Univariate Predictors of a Blood Eosinophil Count of ≥300 Cells/μL in the TASCS Trial Sample

Baseline Variable	Regression Coefficient (95% CI)	P-value
Sex (Male)	0.410 (0.098–0.721)	0.01
Body Mass Index	0.047 (0.012–0.082)	0.009
Post-BD FEV_1 Value (Litres)	0.068 (0.018–0.119)	0.008
FEV_1 Reversibility (mL)	0.095 (0.001–0.188)	0.048
Post-BD FVC Value (Litres)	0.356 (0.195–0.517)	<0.001
Post-BD FVC Value (%predicted)	0.002 (0.001–0.003)	0.005
Respiration Rate	−0.080 (−0.134 – −0.027)	0.003
Blood Creatinine Concentration	0.009 (0.002–0.016)	0.013
Blood White Blood Cell count	0.034 (0.019–0.036)	<0.001
Blood Monocyte Count	0.224 (0.129–0.319)	<0.001
Blood Lymphocyte Count	0.277 (0.127–0.426)	<0.001
Blood Neutrophil Count	0.021 (0.004–0.039)	0.017

Abbreviations: FEV1, forced expiratory volume – 1 second; FVC, forced vital capacity.

participants randomized to placebo. Rates of hospitalization and out-of-hospital use of antibiotics and/or oral corticosteroids due to AECOPD were also both significantly higher in the double-treatment group compared to pooled placebo.

The overall findings of this analysis were unexpected, as existing disease models and in vitro studies had suggested that the proposed synergistic anti-inflammatory action of low-dose theophylline and prednisone would benefit participants with an elevated eosinophil count. Retrospective cohort studies and post-hoc analyses of clinical trials have found that regular administration of inhaled corticosteroid therapy is associated with an inverse relationship between exacerbation risk and frequency and blood eosinophil counts.[9–15] This has formed the basis for the current GOLD recommendation that patients with frequent exacerbations and blood eosinophil counts exceeding ≥300 cells/μL adopt combination pharmacotherapy containing an inhaled corticosteroid added to long acting bronchodilator(s).[2] Though this is congruent with Chinese guidelines,[16,17] inhaled corticosteroid therapy is only used in any capacity by 0–1% of the patient population. By contrast, use of theophylline as a maintenance or rescue medication is prevalent, and is an affordable alternative to the gold standard recommendation of fixed-dose inhaled bronchodilators with an optional ICS component.[18,19]

The results of this analysis are difficult to contextualize and interpret as available literature exploring the characteristics of this region-specific patient subgroup is incomplete. Previous studies have reported some similarities, associating

eosinophilia with elevated monocytes and lymphocytes, but also observing an inverse relationship with blood neutrophils.[20–22] Globally, analyses of the COPDgene, ECLIPSE, SPIROMICS datasets have found variable associations between these inflammatory cells and increased blood eosinophil counts in stable COPD participants – though male predisposition is evident in most studies.[23–26]

While the mechanism for the observed treatment effect is unclear, it is possible that the study participants with eosinophilia defined by a blood eosinophil count ≥300 cells/μL display a hitherto unrecognized clinical phenotype. This is supported by the presence of superior lung function, male predisposition, and concurrently elevated total WBC, monocyte, neutrophil and lymphocyte counts. It is possible that raised eosinophils in the study's Chinese COPD sample, which were associated with a higher overall WBC, may represent a state of low-grade inflammation which is not suppressed by corticosteroids. Another aspect to consider is that the TASCS sample is not representative of typical clinical trials for COPD pharmacotherapies, instead recruiting from a Chinese population with representation from never-smokers and regionally situated patients.[(27)]

Alternatively, it may be that this subset of participants had elevated blood eosinophil counts not originating from an underlying COPD phenotype, but instead an undiagnosed infection at baseline. This would account for the commensurate increases in the overall and individual components of the WBC counts. Subsequently, initiation of steroid-mediated systemic immunosuppression could have provided newly acquired or existing pathogens the opportunity to persist and lead to an exacerbation. This has some precedent, as a recent meta-analysis of seven studies investigating the use of concomitant administration of theophylline with inhaled corticosteroids found that their coadministration may lead to an increased risk of COPD-related hospitalization and mortality in the patient population.[28] Relevant to this may also be evidence from studies such as TORCH, which demonstrated the risk of pneumonia through regular use of inhaled corticosteroids. A recent cohort study reported that rheumatoid arthritis participants prescribed low-dose systemic glucocorticosteroids were significantly more likely to be admitted to hospital for infection.[29,30] With the existing TASCS data, it was not possible to determine if this proposed mechanism is responsible, as no sputum samples were collected, and complete blood counts were not conducted post-randomisation.

Eosinophils are the primary innate immune cell for parasitic infection, so undiagnosed parasitism may be a potential confounder for the false-positive detection of an eosinophilic COPD phenotype. A statement by the "Asian Pacific Society of Respirology" suggests the screening of patients for infection prior to addition of a corticosteroid component to a maintenance pharmacotherapy regimen.[31] Though parasitic infections are endemic in a number of the provinces where recruitment occurred,[32] the randomized trial design and analysis cofactors used would minimize this effect. The rate of eosinophilia observed in the sample was also similar to past COPD studies conducted in China.[33] Observational studies conducted in other regions where gastrointestinal parasites are endemic have found that screening out COPD patients with comorbid infection still leaves a significant proportion of the patient population with eosinophil counts of ≥300 cells/μL of blood.[34,35]

Though these results are intriguing, the interpretation of treatment effect must be considered against some limitations. This was a pre-specified post-hoc analysis that aimed to identify a treatment effect in a subset (n = 325 of 1487) of the trial participants, and was underpowered compared to the primary analysis of the TASCS dataset.[8] Some variance may also be attributable to the differences between the 37 recruiting sites. A relevant example is that sites were permitted to use their own clinical chemistry and blood cell ranges when determining if a participant's values precluded them from trial participation. While this was mitigated using a robust multi-level mixed-effects model adjusted for site as a random effect and region as a fixed effect, it may account for a small portion of study outcome variance. As there are very few studies from Chinese populations that clearly define the different COPD phenotypes, and characteristic eosinophil profiles in the context of their response to treatment, it is also hard to compare and contextualize these results. Given the major burden of disease in China, these studies are urgently required to better define the COPD population in the context of their unique combination of geographic location, environmental exposures, genetics and culturally specific factors.

Conclusion

In summary, this post-hoc analysis of data from the TASCS trial shows that in Chinese COPD participants with an elevated blood eosinophil count, concomitant oral theophylline and prednisone was associated with increased frequency

of acute exacerbations compared to participants receiving placebo. Although a precise explanation for this finding is lacking, the long-term coadministration of these pharmacotherapies is cautioned in this subgroup of COPD patients until further research is conducted.

Data Sharing Statement

Access may be considered by the protocol steering committee and sponsor upon request.

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Disclosure

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