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ORIGINAL RESEARCH

The Effect of Maintenance Treatment with Erdosteine on Exacerbation Treatment and Health Status in Patients with COPD: A Post-Hoc Analysis of the RESTORE Dataset

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Video Abstract

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Purpose: To explore the effect of erdosteine on COPD exacerbations, health-related quality of life (HRQoL), and subjectively assessed COPD severity.

Patients and methods: This post-hoc analysis of the RESTORE study included participants with COPD and spirometrically moderate (GOLD 2; post-bronchodilator forced expiratory volume in 1 second [FEV_1] 50–79% predicted; n = 254), or severe airflow limitation (GOLD 3; post-bronchodilator FEV_1 30–49% predicted; n = 191) who received erdosteine 300 mg twice daily or placebo added to usual maintenance therapy for 12 months. Antibiotic and oral corticosteroid use was determined together with patient-reported HRQoL (St George's Respiratory Questionnaire, SGRQ). Patient and physician subjective COPD severity scores (scale 0–4) were rated at baseline, 6 and 12 months. Data were analyzed using descriptive statistics for exacerbation severity, COPD severity, and treatment group. Comparisons between treatment groups used Student's *t*-tests or ANCOVA as appropriate.

Results: Among GOLD 2 patients, 43 of 126 erdosteine-treated patients exacerbated (7 moderate-to-severe exacerbations), compared to 62 of 128 placebo-treated patients (14 moderate-to-severe exacerbations). Among those with moderate-to-severe exacerbations, erdosteine-treated patients had a shorter mean duration of corticosteroid treatment (11.4 days vs 13.3 days for placebo, $P = 0.043$), and fewer patients required antibiotic treatment with/without oral corticosteroids (71.4% vs 85.8% for placebo, $P < 0.001$). Erdosteine-treated GOLD 2 patients who exacerbated showed significant improvements from baseline in SGRQ total scores and subjective disease severity scores (patient- and physician-rated), compared with placebo-treated patients regardless of exacerbation severity. Among GOLD 3 patients, there were no significant differences between treatment groups on any of these measures.

Conclusion: Adding erdosteine to the usual maintenance therapy of COPD patients with moderate airflow limitation reduced the number of exacerbations, the duration of treatment with corticosteroids and the episodes requiring treatment with antibiotics. Additionally, treatment with erdosteine improved HRQoL and patient-reported disease severity.

Keywords: antibiotic, chronic obstructive pulmonary disease, erdosteine, COPD exacerbation, health-related quality of life, systemic corticosteroid

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Plain Language Summary

People with chronic obstructive pulmonary disease (COPD) can experience episodes of worsening symptoms (cough, breathlessness) of differing severity (mild, moderate, or severe exacerbations), and may need to be treated with antibiotics and/or oral steroids. We looked at the effects of adding an oral drug (erdosteine) to usual daily therapy for 12 months on exacerbation events, severity, treatment, and patient health status. We found that patients with moderate COPD had fewer exacerbations when taking erdosteine and that this was associated with a better health status. The patients with moderate-to-severe exacerbations were also less likely to require treatment with antibiotics or oral steroids. Patients with severe COPD did not show these effects when erdosteine was added to their usual therapy. Our results suggest that regular treatment with erdosteine may reduce exacerbations and improve the health status of some patients with COPD.

Introduction

Acute episodes of symptomatic deterioration (exacerbations) have long been recognized as clinically important events for patients with chronic obstructive pulmonary disease (COPD) and were first used as a clinical trial endpoint over 20 years ago in the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study.[1] Subsequent analyses of interventional and observational studies showed that exacerbations led to sustained worsening of health-related quality of life (HRQoL) and contributed to disease progression.[2,3] Prolonged recovery from an exacerbation was associated with a poorer HRQoL and increased risk of further exacerbations.[4] Treatment of COPD aims to prevent exacerbations and/or shorten their frequency, severity, and/or duration.[5,6]

A pragmatic definition of exacerbations based on worsening symptoms and increased use of treatment was developed for use in clinical trials and has subsequently been applied more widely.[7,8] Moderate episodes were considered to require treatment with antibiotics and/or systemic corticosteroids while severe events require hospitalization. Using this definition, it was shown that long-acting inhaled bronchodilators alone[9] or in combination with inhaled corticosteroids (ICS) could decrease the rate of exacerbations and that this was associated with improvements in health status.[10] Recent data highlight the heterogeneity of these events[11] with differential responses to preventative therapy[12] and differing in clinical courses.[13] The symptomatic episodes managed solely by increases in existing medication were harder to define and required daily diary card monitoring to characterize properly. Nonetheless, these "milder" events are associated with more health care utilization,[14] and worse health status even in individuals who have yet to develop airflow obstruction.[15] Whether treatment that reduces the number of mild exacerbations also improves patient health status is still unclear.

Erdosteine is a mucoactive drug with additional pharmacological properties (anti-inflammatory, antioxidant, bacterial anti-adhesiveness) that is commonly used in the treatment of COPD.[16] The Reducing Exacerbations and Symptoms by Treatment with Oral Erdosteine in COPD (RESTORE) study showed that COPD patients treated with erdosteine with a history of moderate or severe exacerbations had a decreased exacerbation rate and shortened duration of events without alterations in lung function.[16] In a further analysis of these data, we showed that the principal benefits of erdosteine treatment occurred in patients with less severe disease defined spirometrically and where more mild exacerbations occurred. In fact, in these patients there was a 58.3% reduction in the mild exacerbation rate with erdosteine, compared to placebo, irrespective of concurrent treatment with ICS.[17]

In this manuscript, we have further explored these data to better characterize the effect of erdosteine on the moderate-to-severe exacerbations, to determine whether the decrease in exacerbations in moderate COPD led to changes in health status, and whether this was the case for both mild and moderate-to-severe exacerbation events.

Methods

Study Design and Patients

The RESTORE study (NCT01032304) was a Phase III multinational, randomized, double-blind, placebo-controlled study conducted in 10 European countries. Full details of the study design, inclusion and exclusion criteria, ethical approval, and results have been reported elsewhere.[16] Briefly, after a 2-week run-in period with their usual COPD therapy to confirm clinical stability, 467 COPD patients with moderate or severe airflow limitation (grade II/III, GOLD 2007 classification) were randomized to receive either oral erdosteine at a standard approved dose (300 mg twice daily, n = 228) or placebo (n = 239) for 12 months as add-on therapy to their usual COPD treatment. Participants were outpatients

aged 40–80 years, current or ex-smokers (≥10 pack-years), on a stable therapeutic regimen for ≥8 weeks prior to inclusion, and who had experienced ≥2 acute COPD exacerbations requiring medical intervention in the previous 12 months, but with no exacerbations in the preceding 2 months.

The study protocol was approved by local ethics committees as outlined in the primary report and subsequent data analysis.[16,17] In the UK, this was done by the South Sefton Research Ethics Committee. Each participant provided written informed consent prior to study enrolment and the trial was conducted in accordance with the Declaration of Helsinki.

In this post-hoc analysis we reclassified patients participating in the RESTORE study using the spirometry criteria from the GOLD 2022 guidelines.[8] Thus, COPD patients with moderate airflow limitation (GOLD 2) were defined as having a post-bronchodilator forced expiratory volume in one second (FEV_1) between 50% and 79% predicted, and patients with severe airflow limitation (GOLD 3) had a post-bronchodilator FEV_1 between 30% and 49% predicted; both subgroups had a post-bronchodilator fixed ratio FEV_1/forced vital capacity [FVC] <0.70.

Outcomes

A COPD exacerbation was defined as a worsening of symptoms beyond normal day-to-day variation that required a change in regular medication and/or health care resource utilization.[7] Exacerbations were confirmed by the investigators from the variation in daily symptom (dyspnea, cough, sputum) scores, changes in regular medication, use of additional medication or emergency hospitalization for COPD, as recorded in the patient diary. Exacerbation severity was graded as mild, moderate, or severe (Supplementary Table 1) and patients were grouped as having mild or moderate-to-severe exacerbations. Patients may have had more than one exacerbation during the 12-month treatment period: those in the moderate-to-severe exacerbations subgroup may also have had mild exacerbations, but patients in the mild exacerbations subgroup did not have moderate-to-severe exacerbations during the 12 months of treatment. Use of oral corticosteroids and/or antibiotics, and the duration of such treatment for an acute exacerbation was determined from data recorded in the daily diary. All use of oral corticosteroids was converted to prednisolone equivalent doses (Supplementary Table 2).

Subjective Assessments

HRQoL was self-assessed by patients at baseline and after 6 and 12 months of treatment using the St. George's Respiratory Questionnaire (SGRQ), a validated 76-item questionnaire developed to measure health status in patients with chronic airflow limitation.[18] The questionnaire has three domains measuring symptoms, activity limitation, and impact on daily life. The total score is calculated from the domain scores and ranges from 0 (no effect) to 100 (maximum effect), with lower scores corresponding to a better health status. A change of ≥4 points is considered the minimal clinically important difference (MCID) relevant to the patient.[19]

Subject's and Physician's Global Assessment of Disease Severity was assessed at baseline and after 6 and 12 months of treatment. Subjects were asked: "Overall, on a scale 0–4, how troublesome is your lung problem today?" Responses were graded as: 0 = not troublesome at all; 1 = a little troublesome; 2 = moderately troublesome; 3 = very troublesome; 4 = unbearably troublesome. At the same visits, investigators were asked to respond to the following question: "Based on clinical examination and patient interview, how would you rate patient's COPD?" Responses were graded as: 0 = subject with stable COPD, none or minimal symptoms; 1 = subject with stable COPD, occasional symptoms, fully functional; 2 = subject with stable COPD, recurring symptoms, slight functional impact; 3 = subject with stable COPD, frequent moderate to severe symptoms, functionality limited; 4 = subject with stable COPD, constant severe symptoms, functional impairment.

Statistical Analysis

All post-hoc efficacy analyses were conducted using intention-to-treat (ITT) principles on randomized patients who received at least one dose of study treatment and had at least one available post-baseline efficacy evaluation.

Baseline characteristics are reported using descriptive statistics (means and standard deviations [SD] or percentages). Comparisons between treatment groups were performed using the Chi-squared test followed by Fisher's exact test.

Comparisons between COPD severity groups (GOLD 2 vs GOLD 3) were performed using Student's *t*-tests for unpaired samples (if normal distribution) or Mann–Whitney *U*-tests.

SGRQ total scores and patient and physician subjective disease severity scores at baseline, 6 months, and 12 months in patients who experienced exacerbations are presented as mean (95% confidence intervals [CI]) by COPD severity (GOLD 2 or GOLD 3), exacerbation severity (mild or moderate-to-severe), and treatment group (erdosteine or placebo). Changes in trend over time for each treatment group were analyzed using Residual Maximum Likelihood (REML) or least squares method. Comparisons between treatment groups were based on an analysis of covariance (ANCOVA) model including the fixed effects of treatment. The percentage of people showing a decrease in SGRQ total score of at least 4 points was calculated for the GOLD 2 group by exacerbation severity and treatment group.

The percentage of patients with moderate-to-severe exacerbations who used antibiotics and/or oral corticosteroids are reported by COPD severity and treatment group. Comparisons between treatment groups were performed using the Chi-squared test followed by Fisher's exact test. Oral corticosteroid doses are presented as mean (SD) prednisolone-equivalent daily dose and as total dose over 12 months, and comparisons between treatment groups used Student's *t*-tests for unpaired samples. Duration of oral corticosteroid treatment was determined by COPD severity, exacerbation severity, and treatment group. Comparisons between treatment groups was based on an ANCOVA model including fixed effects of treatment.

Statistical analyses were performed using SPSS version 21.0 (IBM, Armonk, NY, USA). A two-sided p-value <0.05 was considered nominally significant for all tests.

Results

In this post-hoc analysis of data from the RESTORE study, 254 patients had COPD with moderate airflow limitation (GOLD 2; post-bronchodilator FEV_1 50–79% predicted) and 191 patients had COPD with severe airflow limitation (GOLD 3; post-bronchodilator FEV_1 30–49% predicted). Of the GOLD 2 patients, 126 received erdosteine and 128 received placebo. In the GOLD 3 subgroup, 89 received erdosteine and 102 received placebo. Figure 1 shows the flow of patients considered in this analysis (ITT population).

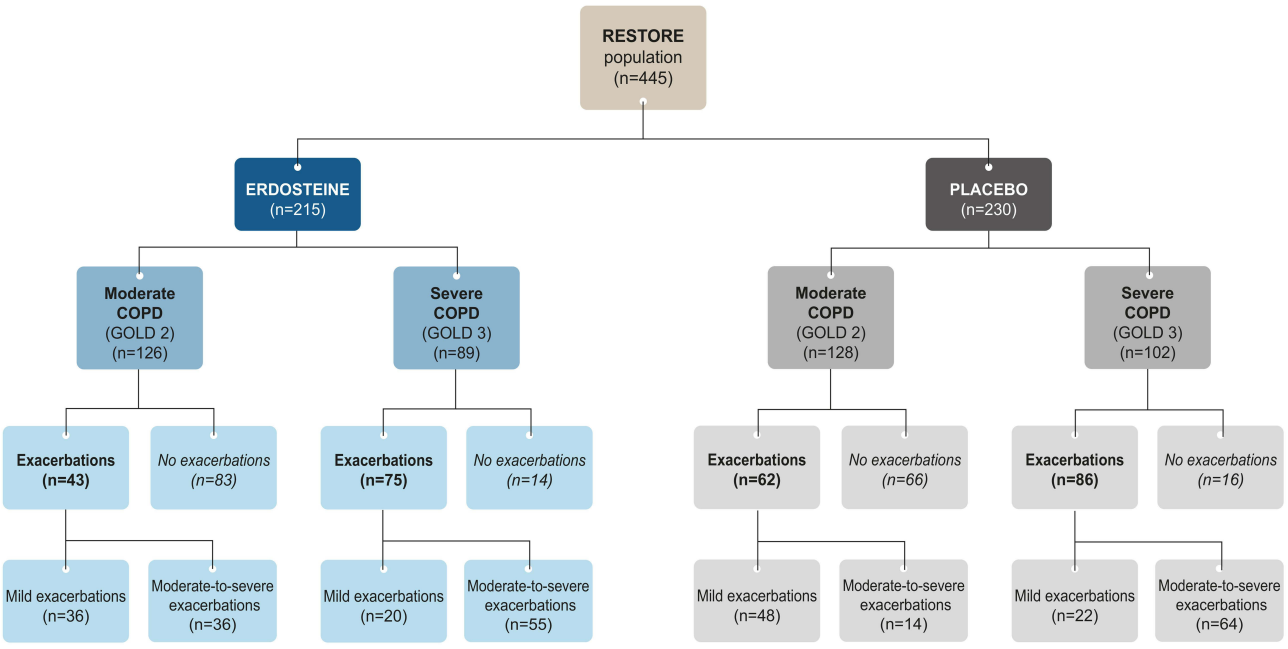

Figure 1 Flow chart of patients in the analysis by treatment group, severity of COPD, exacerbation status, and severity of exacerbations (ITT population). All numbers refer to numbers of patients.

Abbreviations: COPD, chronic obstructive pulmonary disease; GOLD, global initiative for chronic obstructive lung disease; ITT, intention-to-treat.

The baseline demographic and clinical characteristics of the patients did not differ between treatment groups within each subgroup by COPD severity or for the total RESTORE population (Table 1). As expected, the GOLD 2 subgroup had significantly higher FEV_1 and FVC values and significantly fewer patients were using ICS, compared with the GOLD 3 subgroup.

In the GOLD 2 subgroup (n = 254), there were 127 exacerbations in 105 patients during the 12 months of treatment with erdosteine or placebo: 38 were moderate-to-severe exacerbations in 21 patients (7 patients in the erdosteine group and 14 patients in the placebo group), and 89 were mild exacerbations in 84 patients (36 patients in the erdosteine group and 48 patients in the placebo group). In the GOLD 3 subgroup (n = 191), there were 330 exacerbations in 161 patients: 133 moderate-to-severe exacerbations in 119 patients (55 patients in erdosteine group and 64 patients in placebo group), and 197 mild exacerbations in 42 patients (20 patients in erdosteine group and 22 patients in placebo group). The baseline demographic and clinical characteristics of patients with GOLD 2 and GOLD 3 COPD who experienced exacerbations by observed exacerbation severity are shown in Supplementary Tables 3 and 4.

Impact of Erdosteine on Patient Health Status

In the GOLD 2 subgroup, the baseline mean SGRQ total score for those erdosteine-treated patients who experienced exacerbations during follow-up was 38.5 (SD 10.9): the scores were 33.3 (SD 9.0) for those with mild exacerbations and 44.4 (SD 12.3) for those with moderate-to-severe exacerbations. In the corresponding GOLD 2 placebo group, the baseline mean SGRQ total score was 38.8 (SD 11.4) for those who experienced exacerbations: 33.4 (SD 11.2) for those with mild exacerbations and 43.8 (SD 11.8) for those with moderate-to-severe exacerbations. The baseline mean SGRQ total scores for patients with GOLD 3 COPD (all exacerbations) were 50.7 (SD 17.3) and 49.2 (SD 16.7) for the erdosteine and placebo groups, respectively (Supplementary Table 5).

The mean SGRQ total score decreased significantly from baseline over 12 months of treatment with erdosteine but not with placebo in GOLD 2 patients who experienced exacerbations; the decrease in SGRQ total score and between-treatment comparisons were significant regardless of exacerbation severity (Figure 2, Supplementary Table 5). There were no significant changes from baseline in SGRQ total score or between-treatment difference among GOLD 3 patients who experienced exacerbations or for all RESTORE patients with exacerbations (Supplementary Table 5). Of the GOLD

Table 1 Demographic and Baseline Characteristics of Patients (ITT Population)

	GOLD 2 Patients[a] (N = 254)		GOLD 3 Patients[b] (N = 191)		All RESTORE Patients (N = 445)	
	Erdosteine	**Placebo**	**Erdosteine**	**Placebo**	**Erdosteine**	**Placebo**
Patients, n	126	128	89	102	215	230
Age, years	64.8 (7.6)	66.1 (7.3)	62.9 (8.9)	63.1 (8.8)	63.8 (8.3)	64.1 (8.2)
Male, %	65.9	72.7	74.5	73.9	71.8	74.6
BMI, kg/m^2	27.6 (5.0)	28.2 (5.6)	27.0 (4.8)	27.8 (5.1)	27.2 (5.3)	28.0 (5.4)
Smoking status, %						
Current smoker	31.7	28.9	25.8	27.5	27.1	28.0
Ex-smoker	68.3	71.1	74.2	72.5	72.9	72.0
ICS, n (%)	88 (69.8)	91 (71.1)	80 (89.9)*	94 (92.2)*	165 (75.8)	173 (75.2)
FEV_1, L	1.61 (0.35)	1.68 (0.42)	1.26 (0.39)*	1.23 (0.43)*	1.43 (0.40)	1.46 (0.47)
FEV_1, % predicted	59.88 (6.3)	61.08 (6.8)	47.21 (10.83)*	46.72 (11.69)*	51.45 (12.82)	54.38 (13.33)
FVC, L	2.82 (0.66)	2.89 (0.72)	2.59 (0.99)*	2.54 (0.97)*	2.74 (0.93)	2.74 (0.94)
Post-BD FEV_1/FVC, ratio %	58.76 (8.8)	58.00 (8.1)	51.92 (9.88)*	50.81 (10.03)*	54.01 (11.3)	53.26 (10.8)

Notes: Data are presented as mean (standard deviation) unless indicated otherwise. [a]GOLD 2: moderate COPD group, determined post-hoc and based on GOLD 2022 spirometry criteria (FEV_1 50–79% predicted); [b]GOLD 3: severe COPD group, determined post-hoc and based on GOLD 2022 spirometry criteria (FEV_1 30–49% predicted). *$P < 0.05$ vs GOLD 2 group. Categorical variables compared as continuous depending on distribution: Student's *t*-test for unpaired samples (if normal distribution) or Mann–Whitney *U*-test. All comparisons between erdosteine and placebo groups were non-significant.

Abbreviations: BD, bronchodilator; BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, global initiative for chronic obstructive lung disease; ICS, inhaled corticosteroid; ITT, intention-to-treat.

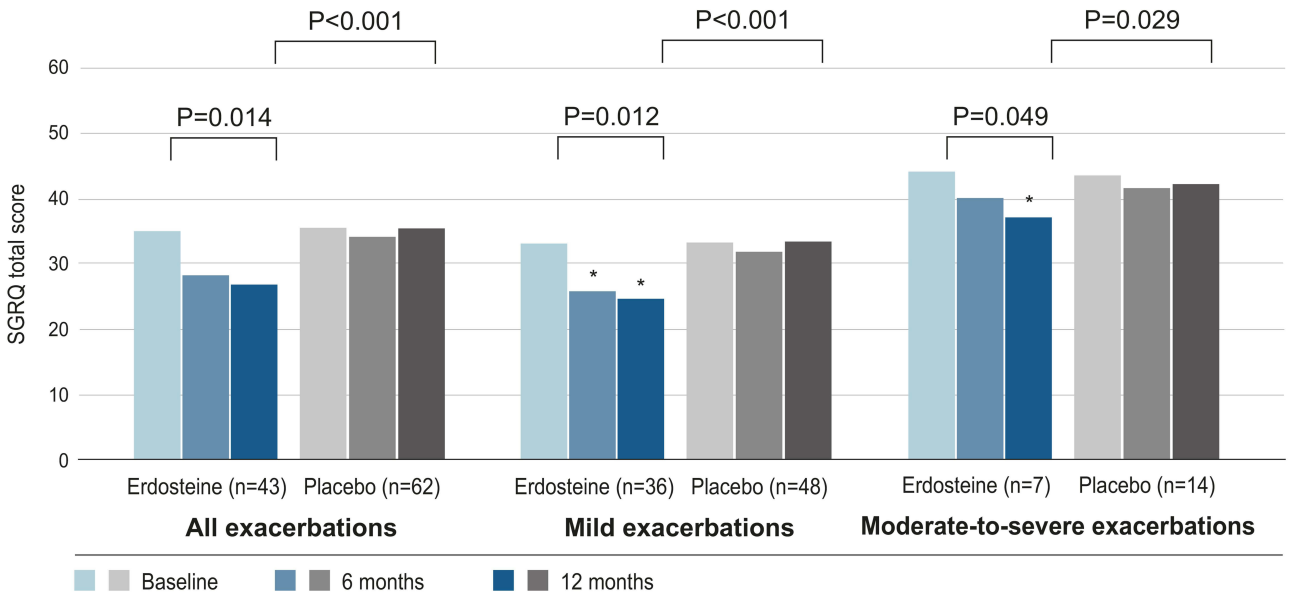

Figure 2 Mean SGRQ total score for GOLD 2 patients with moderate COPD who experienced exacerbations in each treatment group (erdosteine or placebo) and for the subgroups by exacerbation severity (mild or moderate-to-severe). A lower score represents a better HRQoL. Patients may have experienced more than one exacerbation, but those in the mild exacerbations subgroup only experienced mild exacerbations, while those in the moderate-to-severe exacerbations subgroup may also have experienced mild exacerbations. The n value for each treatment group is the number of patients with exacerbations. There were 127 exacerbations overall (89 mild exacerbations and 38 moderate-to-severe exacerbations). Analysis was conducted in the ITT population and based on ANCOVA model including fixed effects of treatment. *P* values given above the columns are for significant changes in trend over time for each treatment and for the treatment comparison; they were analyzed using the Residual Maximum Likelihood or least squares method. *$P < 0.05$ versus placebo at each timepoint.

Abbreviations: ANCOVA, analysis of covariance; COPD, chronic obstructive pulmonary disease; GOLD, global initiative for chronic obstructive lung disease; HRQoL, health-related quality of life; ITT, intention-to-treat; SGRQ, St George's respiratory questionnaire.

2 patients who exacerbated during 12 months of follow-up, a ≥4-point decrease in SGRQ score was seen for 13.9% of erdosteine-treated patients and 4.6% of placebo-treated patients. For those with moderate-to-severe exacerbations, this MCID occurred in a higher proportion of erdosteine recipients (28.5%) than in those taking placebo (7.2%; $P < 0.001$). Among the GOLD 2 patients with mild exacerbations, a ≥4-point decrease in SGRQ score was seen for 11.1% of erdosteine-treated patients and 6.3% of placebo-treated patients ($P = 0.003$).

The scores from the patient's assessment of disease severity (Table 2) show that erdosteine-treated GOLD 2 patients experiencing exacerbations reported a significant reduction in mean disease severity score over time (1.49 at baseline to 1.25 at 12 months, $P = 0.021$) that was significantly different from the scores reported by the placebo group (1.50 at baseline and 1.54 at 12 months, $P < 0.001$ for treatment group comparison). The significant reduction in patient perception of disease severity in erdosteine-treated GOLD 2 patients was seen regardless of the severity of exacerbation. GOLD 3 patients with exacerbations did not report improved subjective severity scores over time or differences between treatment groups (Table 2). Similar results were found for the physician global assessment of disease severity (Supplementary Table 6).

Impact of Erdosteine on Treatment of Moderate-to-Severe Exacerbations

Systemic corticosteroids were used by 89% (125/140) of the RESTORE population to manage exacerbations irrespective of the spirometric severity of their disease. In the GOLD 2 subgroup, systemic corticosteroids were used by a significantly lower proportion of patients receiving erdosteine (85.7%) compared with placebo (92.9%, $P < 0.05$), while 89% of GOLD 3 patients in both treatment groups were treated with oral corticosteroids. Different centers used different corticosteroids (see prednisolone-equivalent doses in Supplementary Table 2). Figure 3 shows the pattern of antibiotic use for moderate-to-severe exacerbation treatment in the RESTORE population. Significantly fewer GOLD 2 patients with moderate-to-severe exacerbations were treated with antibiotics ± oral corticosteroids when they were taking erdosteine (71.4%) as compared to placebo (85.8%, $P < 0.05$). This difference in antibiotic use ± oral corticosteroids

Table 2 Patient Subjective Assessment of Disease Severity Over Time by COPD Severity, Exacerbation Severity and Treatment Group

Exacerbation Severity[a] (Number of Exacerbations)	Treatment	Mean (95% CI) Disease Severity Score (Patient Assessed)			*P*-value for Trend	*P*-value for Treatment Comparison
		Baseline	6 Months	12 Months		
GOLD 2 patients (N = 254)						
All exacerbations (n = 127)	Erdosteine	1.49 (1.14–1.99)	1.37 (1.09–1.99)*	1.25 (0.79–1.95)*	**0.021**	**< 0.001**
	Placebo	1.50 (1.15–2.08)	1.51 (1.15–2.08)	1.54 (1.19–2.11)	0.129	
Mild exacerbations (n = 89)	Erdosteine	1.26 (1.12–1.34)	1.09 (1.04–1.29)*	0.92 (0.72–1.23)*	**0.008**	**< 0.001**
	Placebo	1.29 (1.13–1.37)	1.31 (1.12–1.41)	1.35 (1.15–1.42)	0.218	
Moderate-to-severe exacerbations (n = 38)	Erdosteine	1.87 (1.60–2.04)	1.82 (1.74–2.03)	1.71 (1.62–1.99)*	**0.044**	**0.047**
	Placebo	1.91 (1.82–2.14)	1.89 (1.80–2.15)	1.95 (1.80–2.18)	0.483	
GOLD 3 patients (N = 191)						
All exacerbations (n = 330)	Erdosteine	2.10 (1.81–2.44)	2.03 (1.90–2.36)	2.08 (1.94–2.71)	0.534	0.521
	Placebo	2.04 (1.86–2.47)	2.06 (1.81–2.44)	2.08 (1.94–2.71)	0.102	
Mild exacerbations (n = 197)	Erdosteine	1.89 (1.70–2.15)	1.90 (1.78–2.22)	1.91 (1.82–2.25)	0.547	0.544
	Placebo	1.86 (1.74–2.18)	1.92 (1.80–2.23)	1.93 (1.82–2.24)	0.094	
Moderate-to-severe exacerbations (n = 133)	Erdosteine	2.32 (2.28–2.47)	2.26 (2.14–2.39)	2.29 (2.19–2.82)	0.594	0.601
	Placebo	2.28 (2.14–2.51)	2.34 (2.23–2.68)	2.38 (2.22–2.77)	0.184	
All RESTORE patients (N = 445)						
All exacerbations (n = 457)	Erdosteine	1.69 (1.61–1.96)	1.63 (1.41–1.90)	1.48 (1.41–1.99)*	**0.049**	**0.027**
	Placebo	1.72 (1.45–1.96)	1.69 (1.43–1.96)	1.65 (1.50–1.84)	0.076	
Mild exacerbations (n = 286)	Erdosteine	1.52 (1.46–1.70)	1.46 (1.37–1.67)	1.41 (1.37–1.84)*	**0.042**	**0.029**
	Placebo	1.49 (1.42–1.69)	1.50 (1.41–1.88)	1.48 (1.39–1.83)	0.423	
Moderate-to-severe exacerbations (n = 171)	Erdosteine	1.94 (1.66–2.24)	1.92 (1.59–2.21)	1.91 (1.66–2.29)	0.541	0.453
	Placebo	1.95 (1.69–2.28)	1.95 (1.62–2.24)	1.91 (1.66–2.29)	0.528	

Notes: Data are presented as mean (95% CI). Scores range from 0–4, with higher scores representing worse subjective disease severity. [a]Patients may have experienced more than one exacerbation during the 12 months of treatment; they were grouped as having mild or moderate-to-severe exacerbations. Patients in the moderate-to-severe exacerbations subgroup may also have had mild exacerbations, but patients in the mild exacerbations subgroup did not have moderate-to-severe exacerbations during the 12 months of treatment. The analysis was conducted in the ITT population and was based on an ANCOVA model including the fixed effects of treatment. Changes in trend over time were analyzed using the REML or least squares method. *P*-values in bold are considered significant (< 0.05). *$P < 0.05$ vs placebo at each time point.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; GOLD, global initiative for chronic obstructive lung disease; ITT, intention-to-treat; REML, residual maximum likelihood.

between treatment groups was also seen in GOLD 3 patients (84.5% in erdosteine group vs 89.6% in placebo group, $P < 0.05$).

In the GOLD 2 subgroup, the number of patients was similar in the erdosteine and placebo groups (Table 1). Among those GOLD 2 patients who experienced moderate-to-severe exacerbations, the mean total dose of oral corticosteroids over the 12-month study period was significantly lower for erdosteine-treated patients (251.9 mg) versus those receiving placebo (320.5 mg, $P < 0.001$), although the mean daily dose of oral corticosteroid treatment over the same time period did not differ between the groups (Table 3). The difference in total corticosteroid dose between the erdosteine and placebo groups was due to a significantly shorter treatment duration with oral corticosteroids for moderate-to-severe

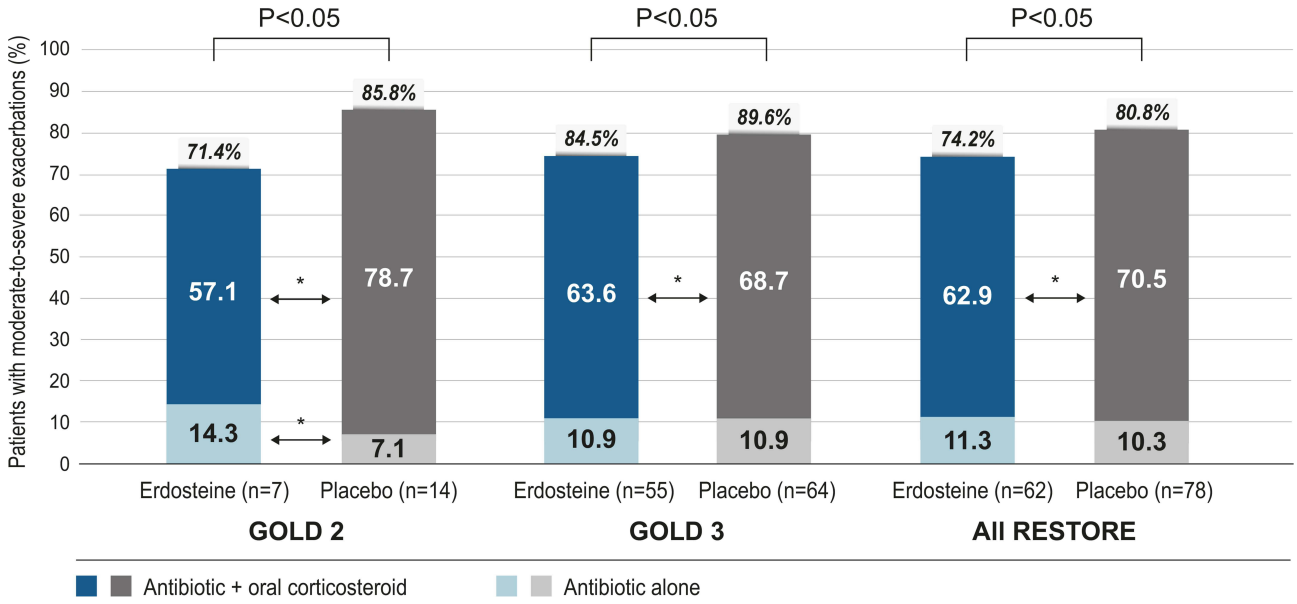

Figure 3 Proportion of patients with moderate-to-severe exacerbations who used antibiotics alone and with oral corticosteroids by disease severity (GOLD 2 or 3) and treatment group. The percentage value in italics above each stacked bar is the total percentage of patients treated with antibiotics (with or without oral corticosteroids); the remaining patients with moderate-to-severe exacerbations received oral corticosteroids alone. The *P* values above the columns are for the comparisons of erdosteine versus placebo for the total percentage of patients treated with antibiotics. The asterisks between columns represent *$P < 0.05$ for erdosteine versus placebo groups within each antibiotic treatment group (antibiotic + oral corticosteroid or antibiotic alone). Analysis used a Chi-square test followed by Fisher's exact test.
Abbreviation: GOLD, global initiative for chronic obstructive lung disease.

exacerbations (mean 11.4 days vs 13.3 days, $P = 0.043$). In the GOLD 3 subgroup, the oral corticosteroid dose (total dose or average daily dose) and treatment duration did not differ between the erdosteine and placebo groups.

Discussion

Much of our understanding about COPD exacerbations and their prevention has been driven by the results of treatment trials and this further analysis of the RESTORE dataset contributes to this process. Early intervention in COPD patients could lead to beneficial effects on disease progression and clinical outcomes; the early treatment might be reasonable

Table 3 Oral Corticosteroid Total Dose and Average Daily Dose (Prednisolone-Equivalents) Over 12 Months in Patients Experiencing Moderate-to-Severe Exacerbations by COPD Severity and Treatment Group

Corticosteroid Dose	Severity of COPD	Prednisolone-Equivalent Dose (mg)				*P*-value[a]
		Erdosteine		Placebo		
		n	Mean (SD)	n	Mean (SD)	
Total dose over 12 months	GOLD 2	6	251.9 (31.3)	13	320.5 (33.9)	**< 0.001**
	GOLD 3	49	491.5 (39.1)	57	507.6 (40.2)	0.761
Average daily dose over 12 months[b]	GOLD 2	6	22.1 (3.5)	13	24.1 (3.2)	0.352
	GOLD 3	49	33.9 (3.7)	57	34.3 (3.6)	0.541

Notes: Data are presented as mean (SD). n = number of exacerbating patients treated with systemic corticosteroids. [a]Student's *t*-test for unpaired samples. *P*-values in bold are considered significant (< 0.05). [b]Calculated as the total dose divided by the mean duration of treatment (in days).
Abbreviations: COPD, chronic obstructive pulmonary disease; GOLD, global initiative for chronic obstructive lung disease; SD, standard deviation.

with the aim of achieving better clinical outcomes in COPD, ameliorating the decline in lung function, and improving the health status.[20] Regular early treatment with erdosteine, as add-on therapy, showed a significant effect on rate and duration of exacerbations.[16]

Patients who had a moderate-to-severe exacerbation while taking erdosteine were less likely to receive antibiotics and had a lower requirement for oral corticosteroids than those taking placebo, especially if they had moderate airflow obstruction when stable The health status of GOLD 3 patients with severe COPD was worse than in those with GOLD 2 moderate disease and was uninfluenced by erdosteine. By contrast, erdosteine use was associated with better health status in GOLD 2 patients who experienced an exacerbation, and this was supported by the subjective global assessments of disease severity scored blinded to maintenance treatment. These observations have clinical relevance.

For many years, treatment trials and observational studies have used a health care utilization definition of exacerbation in identifying differing clinical courses of these acute episodes.[13] However, it is now clear that episodes that are not treated with antibiotics and corticosteroids still impact the patient's health status,[14] while some preventive treatments (ICS) mainly act by decreasing episodes where corticosteroids are used[15] or are less effective as airflow obstruction worsens.[21,22] Anti-inflammatory therapies like ICS and the phosphodiesterase-4 inhibitor roflumilast are most effective in patients with higher blood eosinophil counts.[23,24] Erdosteine has a different anti-inflammatory action and its effects on exacerbation prevention are unrelated to the blood eosinophil count.[17] Erdosteine may enhance the effectiveness of co-administered antibiotics in vivo and when given as a treatment for COPD exacerbations, by a variety of mechanisms including effects on bacterial adhesiveness and increasing sputum antibiotic concentrations.[25–27] In our analysis, fewer patients required antibiotic treatment when they experienced an exacerbation if erdosteine was used as maintenance therapy, although the reason for this cannot be definitively addressed with the data available. The episodes treated with oral corticosteroids were managed similarly in terms of the daily dose but the overall corticosteroid exposure was reduced as the exacerbations were shorter when erdosteine was used. Decreasing the patient's exposure to systemic corticosteroids is an important goal of management and the results observed with erdosteine in this study suggest that this drug could be helpful in this regard, at least in patients with less severe airflow obstruction.

The association between worse health status and a higher exacerbation frequency is well established for both reported and unreported exacerbations.[14,28] The focus on episodes treated with antibiotics and/or corticosteroids has led to the impression that only these episodes are important. Our data suggest that this is not so, at least among patients with moderate COPD who experience an exacerbation. In our GOLD 2 group, where similar numbers received erdosteine or placebo, the SGRQ scores over the year differed between the exacerbators in these two groups. Among the erdosteine-treated GOLD 2 patients who had a moderate-to-severe exacerbation event, health status had improved significantly by 6 months after randomization and this change was maintained at 12 months compared to those who exacerbated while using placebo. The same was observed for patients with mild exacerbations. These findings were also supported by the subjective global assessment questions, which identified reduced disease severity in the erdosteine-treated GOLD 2 group, regardless of exacerbation severity. The health status of exacerbators taking placebo was stable in moderate disease but improved with erdosteine, with approximately 14% of erdosteine-treated GOLD 2 patients reaching and maintaining the conventional 4-point threshold of clinical significance in SGRQ score over one year. Whether this difference reflected the shorter duration of these exacerbation events or the conversion of more severe events into less severe ones cannot be resolved here. However, there was a clear difference in the behavior of the moderate and severe disease groups. In the latter, exacerbations were more frequent, involved both mild and moderate-to-severe episodes in the same individual, and showed no impact of erdosteine on patient health status. Whether these differences in the response to an exacerbation reflect differences in the triggers to exacerbation or the host response to the event requires further prospective study.

Our study has both strengths and limitations. The RESTORE population was well characterized with both diary card data and an agreed prospective classification of exacerbations based on treatment given. The lack of side effects associated with erdosteine[16] helped with patient retention in the trial and there was no evidence of differential dropout, something which has complicated the interpretation of other trials.[29] Although our treatment groups were well matched at baseline, we did not adjust further for potential covariates of interest given the relatively small sample size available in each arm of the study. We did not pre-specify criteria for the way in which exacerbations should be managed but left this

to the clinician's usual practice. We recognize that different countries adopt different policies to the selection of antibiotics and the dose of oral corticosteroids used in exacerbation management, but we do not believe that these differences introduced a systematic bias into our data. We used the SGRQ as our principal measure of health status, although the validity of our observations of a differential effect in moderate and severe COPD are supported by the patient and physician global health assessments. Although less robustly validated, these simple clinically applicable tools showed consistency with each other and with the longer SGRQ tool, supporting the usefulness of rapid clinical assessment in evaluating patient health status. However, our study was relatively small compared with other intervention studies and the analyses performed in this manuscript were all post hoc evaluations; thus, the results presented are not conclusive and need to be interpreted with caution, but they do allow the generation of hypotheses that can be tested in future studies.

This further analysis of the RESTORE data set confirms the heterogeneity of exacerbation events which are defined by their differing needs for medical treatment. Patients who have moderate COPD not only have fewer exacerbations when taking erdosteine, but also are less likely to require antibiotic treatment in those that do occur. Furthermore, their overall exposure to systemic corticosteroids of all types is less as the events needing treatment are briefer and less frequent. Measurable improvements in health status are seen in both mild and moderate-to-severe exacerbations in patients who still go on to exacerbate and these are recognizable to both the patient and their doctors, emphasizing the need to not only reduce the number of exacerbations, but also the duration of the ones that do occur. The lack of an impact of erdosteine in patients with more severe disease also indicates that not all exacerbations are the same and that different factors drive the clinical presentation of these events at different stages in the natural history of COPD. Importantly for our understanding of COPD exacerbations, mild exacerbations do affect patient health status, and their reduction following chronic treatment with erdosteine is associated with improved health status that is noticeable to both patients and their physicians. Managing these mild-to-moderate episodes should not be neglected and our data suggest that regular treatment with erdosteine, a drug that is orally active and well tolerated may be a useful treatment in early disease.

Abbreviations

ANCOVA, analysis of covariance; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, global initiative for chronic obstructive lung disease; HRQoL, health-related quality of life; ICS, inhaled corticosteroid; ITT, intention-to-treat; MCID, minimal clinically important difference; REML, residual maximum likelihood; RESTORE, reducing exacerbations and symptoms by treatment with oral erdosteine in COPD; SD, standard deviation; SGRQ, St George's respiratory questionnaire.

Data Sharing Statement

The data included in this paper are from a post hoc analysis of the RESTORE study and are not publicly available.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the manuscript; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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