Rescue Medication Use as an Indicator of Symptom Burden in Patients With COPD: A Post Hoc Analysis of the EMAX Trial

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EMAX TRIAL

Kerwin EM[1], Bjermer L[2], Maltais F[3], Boucot IH[4], Naya IP[5], Tombs L[6], Jones PW[4], Compton C[4], Lipson DA[7], Vogelmeier CF[8]

[1]Clinical Research Institute of Southern Oregon, Medford, OR, USA; [2]Respiratory Medicine and Allergology, Lund University, Lund, Sweden; [3]Centre de Pneumologie, Institut universitaire de cardiologie et de pneumologie de Québec, Université Laval, Québec, QC, Canada; [4]GSK, Brentford, Middlesex, UK; [5]GSK, Brentford, Middlesex, UK (at the time of the study), RAMAX Ltd, Bramhall, Cheshire, UK; [6]Precise Approach Ltd, contingent worker on assignment at GSK, Stockley Park West, Uxbridge, Middlesex, UK; [7]Respiratory Clinical Sciences, GSK, Collegeville, PA, USA, and Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [8]Department of Medicine, Pulmonary and Critical Care Medicine, University Medical Center Giessen and Marburg, Philipps-Universität Marburg, Germany, Member of the German Center for Lung Research (DZL), Marburg, Germany

Background

- Frequent rescue use is associated with an increased risk of COPD exacerbations and hospitalizations.[1–3]
- Assessment of rescue medication use may therefore be a useful marker of disease severity in both clinical trials and routine clinical practice.
- In this post hoc analysis of the Early MAXimization of bronchodilation for improving COPD stability (EMAX) trial[4], it was hypothesized that patients with higher rescue medication use were more symptomatic. The objective was to explore the relationship between baseline rescue medication use and daily Evaluating Respiratory Symptoms–COPD (E-RS) total score, the risk of a clinically important deterioration (CID), and the risk of a composite exacerbation and study treatment withdrawal endpoint.

Methods

- In the double-blind, parallel-group EMAX trial, patients with symptomatic COPD and low exacerbation risk not receiving inhaled corticosteroids were randomized 1:1:1 to umeclidinium/vilanterol (UMEC/VI) 62.5/25 mcg once daily, UMEC 62.5 mcg once daily, or salmeterol (SAL) 50 mcg twice daily for 24 weeks.[4]
- E-RS and rescue medication use were recorded daily and analyzed a priori at 4-weekly intervals. E-RS scores were stratified post hoc by rescue medication use (puffs/day) quartiles at baseline and at Weeks 21–24 to reflect the relationship between rescue medication use and symptoms at each time point.
- The composite CID endpoint was defined prospectively as a first moderate or severe exacerbation, and/or a COPD Assessment Test (CAT) deterioration (≥2 units from baseline), and/or a and/or a self-administered computerized-Transition Dyspnea Index (SAC-TDI) deterioration (≥1 unit decrease from baseline), and/or a St George's Respiratory Questionnaire (SGRQ) deterioration (≥4 units from baseline).
- Hazard ratios (HR) were calculated to assess the effect of for the relationship between baseline rescue medication use on CID, and an exacerbation and study treatment withdrawal combined endpoint (defined post hoc) up to Day 168.
  - CID HR were calculated using a Cox proportional hazards model with covariates of treatment, number of bronchodilators per day during run-in, geographical region, baseline rescue medication use quartile, baseline CAT score, baseline SGRQ score and Baseline Dyspnea Index focal score.
  - For the exacerbation/study treatment withdrawal composite endpoint, HR were calculated with a Cox proportional hazards model with covariates of treatment, number of bronchodilators per day during run-in and geographical region.

Results

Symptom burden by rescue use

- Patients with higher baseline rescue medication use (puffs/day) had a greater symptom burden at baseline according to mean E-RS total score (**Figure 1**).
- Although rescue medication use decreased from baseline during the treatment period in all treatment arms, the relationship between mean rescue medication use (puffs/day) and mean E-RS total score was maintained at Weeks 21–24 (**Figure 2**).
  - No differences were observed between treatment arms.

On-treatment rescue use by baseline rescue use

- There was a trend towards higher on-treatment rescue medication use at Weeks 21–24 in patients with high rescue medication use at baseline (**Figure 3**).

CID and exacerbation/treatment withdrawal by baseline rescue use

- The risk of a CID and the risk of the composite endpoint for an exacerbation or study treatment withdrawal were significantly lower for patients with baseline rescue medication use <0.2 puffs/day versus ≥1.5 puffs/day (**Table 2**).

Table 1. Baseline characteristics

Characteristic	Rescue medication use <1.5 puffs/day (n=1206)	Rescue medication use ≥1.5 puffs/day (n=1212)	ITT (N=2425)
Age, years, mean (SD)	65.7 (8.3)	63.5 (8.5)	64.6 (8.5)
Female, n (%)	454 (38)	529 (44)	988 (41)
Current smoker at screening, n (%)	538 (45)	660 (54)	1203 (50)
Smoking pack-years, mean (SD)	48.7 (26.4)	48.2 (26.6)	48.4 (26.5)
No maintenance treatment during run-in, n (%)	309 (26)	439 (36)	749 (31)
Moderate COPD exacerbation in prior year,* n (%)	202 (17)	188 (16)	393 (16)
Post-albuterol % predicted FEV_1, mean (SD)	57.8 (12.2)	53.1 (12.8)	55.4 (12.7)
% reversibility to albuterol, mean (SD)	8.7 (11.0)	12.2 (14.7)	10.5 (13.1)
Baseline E-RS total score, mean (SD)	8.7 (5.2)	12.5 (5.6)	10.6 (5.7)
Baseline CAT score, mean (SD)	17.6 (5.5)	20.8 (6.3)	19.2 (6.1)
Baseline SGRQ total score, mean (SD)	40.1 (15.0)	49.3 (15.9)	44.7 (16.2)
Baseline rescue medication, puffs/day, mean (SD)	0.39 (0.4)	3.91 (2.4)	2.2 (2.5)

*Number of exacerbations requiring oral or systemic corticosteroids and/or antibiotics (moderate) in 12 months prior to screening (patients with >1 moderate exacerbation or with a severe exacerbation [requiring hospitalization] were excluded).

Figure 1. Baseline E-RS total score by quartiles of rescue medication use at baseline

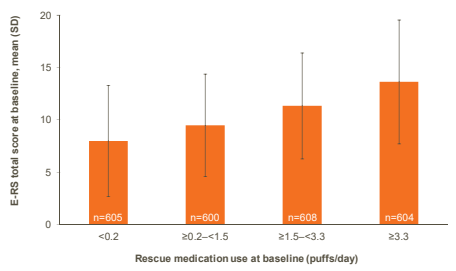

Figure 2. E-RS total score at Weeks 21–24 by on-treatment rescue medication use at Weeks 21–24, by treatment arm

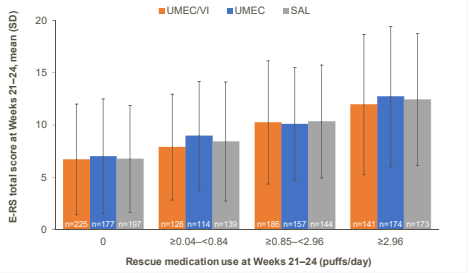

Figure 3. On-treatment rescue medication use at Weeks 21–24 by baseline rescue medication use (with a magnified insert of the main cluster)

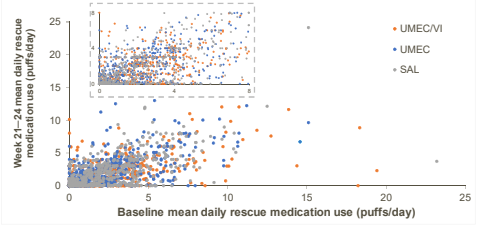

Table 2. CID and exacerbation/study treatment withdrawal by baseline rescue medication use quartile

	Baseline rescue medication use (puffs/day)		
	≥0.2–<1.5	≥1.5–<3.3	≥3.3
Risk reduction with <0.2 puffs/day, % (95% CI)			
CID	2 (-13, 15); *P*=0.788	19 (7, 30); *P*=0.004	23 (10, 34); *P*<0.001
Exacerbation/study treatment withdrawal	15 (-7, 33); *P*=0.163	29 (11, 44); *P*=0.003	32 (15, 46); *P*<0.001

Conclusions

- Mean daily rescue medication use is associated with mean daily symptom burden in patients with COPD.
- Higher baseline rescue medication use is associated with an increased risk of CID and exacerbation/study treatment withdrawal.
- These findings support the use of rescue medication use as a marker of symptom burden and risk of disease worsening in clinical practice and as an endpoint in clinical trials.

References

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