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Ⓞ The Effect of Acclidinium on Symptoms Including Cough in Chronic Obstructive Pulmonary Disease: A Phase 4, Double-Blind, Placebo-controlled, Parallel-Group Study

To the Editor:

Cough and sputum production are very common and troublesome symptoms for patients with chronic obstructive pulmonary disease (COPD) (1), and those symptoms are

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associated with lung function decline, increased exacerbation risk, and poor prognosis (2–4). To date, few clinical studies have investigated the efficacy of a long-acting muscarinic antagonist (LAMA) on cough (5, 6). Acclidinium is a LAMA approved as a twice-daily maintenance bronchodilator treatment for patients with COPD (7). This study assessed the efficacy of acclidinium on symptoms, including cough, in patients with moderate COPD. This was a phase 4, double-blind, placebo-controlled, parallel-group study (clinical trial registered with www.clinicaltrials.gov: NCT02375724) in 30 centers across five European countries between March 23, 2015, and November 17, 2015. Patients were randomly assigned 1:1 to receive twice-daily acclidinium 400 μ g or placebo, administered via a multidose, dry powder inhaler (Genuair/Pressair, a registered trademark of the AstraZeneca group of companies, for use within the United States as Pressair and as Genuair within all other licensed territories). The study comprised a 1- to 2-week run-in period followed by an 8-week treatment period. Efficacy endpoints were measured at Week 4 and Week 8; the data over the course of 8 weeks are shown as an average of the scores measured at Week 4 and Week 8. Patients were aged at least 40 years with moderate COPD (post-bronchodilator FEV₁ \geq 50% and <80% predicted; FEV₁/FVC <70%). The primary endpoint was change from baseline in Evaluating Respiratory Symptoms in COPD (E-RS:COPD, formerly the Exacerbations of Chronic Pulmonary Disease Tool [EXACT]-Respiratory Symptoms Scale [E-RS; <http://www.exactproinitiative.com/instrument-descriptions/>]), is owned by Evidera; permission to use this instrument may be obtained from Evidera [<http://www.exactproinitiative.com/instrument-descriptions/exactpro@evidera.com>]) total score over the course of 8 weeks (minimal clinically important difference [MCID], 2.0) (8). Secondary efficacy endpoints were change from baseline in E-RS cough and sputum domain score over the course of 8 weeks (MCID, 0.7) (8) and change from baseline in Leicester Cough Questionnaire (LCQ; MCID, 1.3) (9) at Week 8. Exploratory endpoints included change from baseline in COPD Assessment Test (CAT) score (MCID, 2.0) (10), cough severity visual analog scale (VAS) score, E-RS total score, and E-RS cough and sputum domain score at Week 4 and Week 8, and E-RS breathlessness (MCID, 0.1) and chest domain scores (MCID, 0.7) (8) at Week 4 and Week 8 and over the course of 8 weeks. A *post hoc* analysis stratified patients by baseline cough severity (VAS; >30 mm, more severe; \leq 30 mm, less severe) to assess the effect of acclidinium on cough-related endpoints. All patients provided written informed consent; study protocols and amendments were approved by local ethics committees. The primary endpoint was analyzed using a mixed model for repeated measures.

Overall, 269 patients were randomized; all had chronic bronchitis, 135 received acclidinium, and 134 received placebo. Sixty percent of patients were male, 64% were current smokers, and mean age was 62 years, with mean post-bronchodilator FEV₁ 64.2% predicted. In addition, patients had previously received short-acting β_2 -agonist (74%) and LAMA (26%). Mean baseline E-RS breathlessness, cough and sputum, and chest domain scores were 6.0, 3.7, and 2.9, respectively, and total E-RS was 12.5. Baseline CAT and LCQ scores were 19.4 and 14.5, respectively.

Significant improvements in E-RS total score were observed with acclidinium versus placebo (Figure 1). Acclidinium

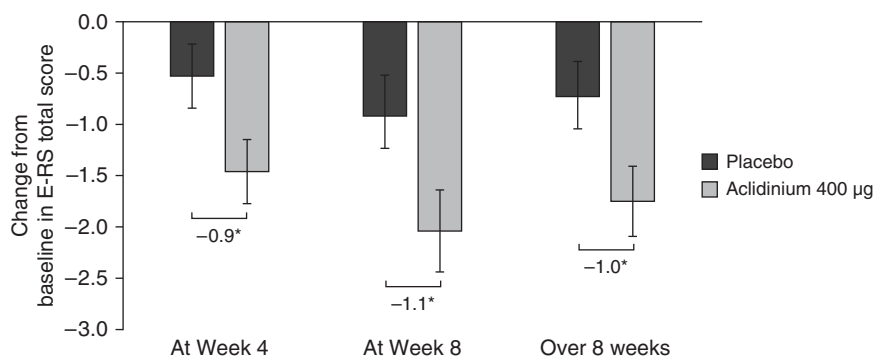


Figure 1. Change from baseline in E-RS total score for acclidinium 400 µg versus placebo (intent-to-treat population). * $P < 0.05$ versus placebo. Data are least squares mean \pm SE. COPD=chronic obstructive pulmonary disease; E-RS=Evaluating Respiratory Symptoms in COPD (E-RS:COPD).

significantly improved E-RS cough and sputum domain scores versus placebo at Week 8 but not at Week 4 or over the course of 8 weeks (Table 1). For E-RS breathlessness domain score, acclidinium provided statistically significant improvements versus placebo at all time points (Table 1). Changes in LCQ total score for acclidinium versus placebo were not statistically significant at any time point (Table 1). Improvements in CAT and E-RS chest domain scores were numerical only (Table 1), as were changes in cough severity (VAS; at Week 4, -0.7 ; at Week 8, -1.1 ; over the course of 8 weeks, -0.9). In total, 264 patients were stratified by cough severity (more severe, 123 patients; less severe, 141 patients). In patients with more severe cough, significant improvements were observed in E-RS total score at

Week 4, and cough and sputum domain scores at each time point (Table 1). Numerical differences versus placebo were observed in LCQ and E-RS breathlessness and chest domain scores, at Weeks 4 or 8, in patients with more severe cough. Statistically significant improvements were seen for patients with more severe cough versus placebo in CAT score at Weeks 4 and 8 (Table 1). No significant differences were observed for any outcome in patients with less severe cough.

Overall, acclidinium significantly improved a range of daily COPD symptoms (including cough and sputum) versus placebo. Improvements in respiratory-specific quality-of-life measures (LCQ and CAT) did not reach statistical significance for acclidinium versus placebo in the total patient population. Baseline LCQ values in

Table 1. Summary of Efficacy for Acclidinium versus Placebo (Intent-to-Treat Population)

	Baseline Cough Any VAS	Baseline Cough VAS >30 mm (More Severe)	Baseline Cough VAS \leq 30 mm (Less Severe)
E-RS total score			
At Week 4	-0.9 (0.4)*	-1.3 (0.6)*	-0.6 (0.6)
At Week 8	-1.1 (0.6)*	-1.2 (0.8)	-1.1 (0.8)
Over 8 wk	-1.0 (0.5)*	-1.2 (0.7)	-0.8 (0.6)
E-RS cough and sputum domain			
At Week 4	-0.1 (0.1)	-0.3 (0.2)*	0.1 (0.2)
At Week 8	-0.3 (0.2)*	-0.5 (0.2)*	-0.2 (0.2)
Over 8 wk	-0.2 (0.1)	-0.4 (0.2)*	-0.1 (0.2)
LCQ			
At Week 4	0.1 (0.3)	0.6 (0.4)	-0.1 (0.4)
At Week 8	-0.1 (0.3)	0.4 (0.4)	-0.4 (0.4)
CAT total score			
At Week 4	-0.7 (0.6)	-2.2 (0.8)*[†]	0.5 (0.8)
At Week 8	-0.6 (0.6)	-2.3 (0.9)*[†]	1.0 (0.9)
E-RS breathlessness domain			
At Week 4	-0.6 (0.2)*	-0.7 (0.3)	-0.5 (0.3)
At Week 8	-0.6 (0.3)*	-0.5 (0.4)	-0.7 (0.4)
Over 8 wk	-0.6 (0.3)*	-0.6 (0.4)	-0.6 (0.4)
E-RS chest symptoms domain			
At Week 4	-0.2 (0.1)	-0.3 (0.2)	-0.2 (0.2)
At Week 8	-0.2 (0.2)	-0.2 (0.2)	-0.2 (0.2)
Over 8 wk	-0.2 (0.1)	-0.3 (0.2)	-0.2 (0.2)

Definition of abbreviations: CAT=COPD Assessment Test; COPD=chronic obstructive pulmonary disease; E-RS=Evaluating Respiratory Symptoms in COPD (E-RS:COPD); LCQ=Leicester Cough Questionnaire; VAS=visual analog scale.

Data are least-squares mean (SE) change from baseline for acclidinium 400 µg versus placebo. Analyzed using a mixed model for repeated measures (covariates: baseline, and age; factors: treatment group, sex, smoking status, visit, and treatment-by-visit interaction). The 30-mm VAS threshold value represented the median value of VAS baseline cough severity score and provided an almost equal split in the patient population. Bold indicates data points that are statistically significant. * $P < 0.05$.

[†]Treatment difference was greater than the minimal clinically important difference (10).

the total population suggested that the impact of symptoms on quality of life was minimal, possibly because of the number of patients with mild cough. Safety outcomes were consistent with those previously reported (11).

Post hoc analyses showed that for patients with more severe cough, aclidinium provided greater improvements versus placebo in E-RS cough and sputum domain scores and CAT score. These patients had higher baseline CAT and E-RS total and domain scores than patients with less severe cough, and a mean LCQ of 12.7, indicating prominent cough symptoms. In contrast to the total population, when patients were stratified by cough severity, there was a numerical trend toward improvement in LCQ in patients with more severe cough versus less severe cough. This suggests baseline cough severity could be an important symptomatic marker for treatment response, and VAS score may reflect some mechanisms driving cough and sputum production in COPD, and specifically those most responsive to aclidinium treatment (12).

One limitation was that this study was powered for E-RS total score and E-RS cough and sputum domain, but not for CAT or LCQ scores. As the LCQ and CAT instruments are designed to capture disease effect rather than severity, these tools may not be as sensitive to symptom changes compared with those specifically designed for symptom severity, such as E-RS. In addition, only patients with moderate COPD were included; therefore, further studies in a population with more severe COPD would be beneficial.

In this study, which was one of the first studies to assess the effect of a LAMA on cough outcomes in patients with COPD, aclidinium 400 µg significantly improved a range of daily symptoms, including cough, in symptomatic patients with moderate COPD compared with placebo. In addition, a subgroup of patients with more severe cough symptoms gained a distinct and early benefit from aclidinium in a number of cough-related endpoints. Therefore, routine evaluation of cough symptoms (in addition to breathlessness) may be of benefit in the treatment management of some patients with moderate COPD. ■

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Jaclyn A. Smith, M.B. Ch.B., Ph.D.*
Manchester University NHS Foundation Trust
Manchester, United Kingdom
and
University of Manchester
Manchester, United Kingdom

Lorcan McGarvey, M.D.
Queen's University Belfast
Belfast, United Kingdom

Alyn H. Morice, M.D.
Castle Hill Hospital
Cottingham, United Kingdom

Surinder S. Biring, M.B. Ch.B., M.D.
King's College London
London, United Kingdom
and
King's College Hospital
London, United Kingdom

Jadwiga A. Wedzicha, M.D.†
Imperial College London
London, United Kingdom

Massimo Notari, M.D.
A. Menarini Farmaceutica Internazionale s.r.l.
Florence, Italy

Antonio Zapata, M.D.
Laboratorios Menarini
S.A. Badalona, Spain

Rosa Segarra, B.Sc.
Beatriz Seoane, B.Sc., M.Sc.
Diana Jarreta, B.Chem.
R&D Centre, AstraZeneca PLC
Barcelona, Spain

ORCID ID: 0000-0001-8837-4928 (J.A.S.).

*Corresponding author (e-mail: jacky.smith@manchester.ac.uk).

†J.A.W. is Editor-in-Chief of *AJRCCM*. Her participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

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Ⓞ Delaying Renal Replacement Therapy Could Be Harmful in Patients with Acute Brain Injury

To the Editor:

We read with interest the article by Gaudry and colleagues on the recent advances regarding the timing of the initiation of renal replacement therapy (RRT) for acute kidney injury (AKI) in critically ill patients (1). The authors conducted the two most recent large-scale studies in this area (2, 3) with concordant results, and propose a potential algorithm for RRT indication and timing. Schematically, their proposal is that unless severe complications related to AKI occur (e.g., hyperkalemia, severe metabolic acidosis, severe fluid overload with pulmonary edema, or neurological symptoms associated with uremic encephalopathy), RRT should be postponed. The use of this strategy did not change the mortality rate of general critically ill patients or those with severe septic shock, and was associated with reduced use of RRT, suggesting a benefit for the “delayed” initiation strategy. The authors should be commended for conducting these studies, which will surely impact the daily practice of ICU physicians. However, we would like to draw attention to a subset of patients who may not benefit from such a delay. Patients with acute brain injury and at risk for cerebral edema and elevated intracranial pressure (e.g., patients with brain trauma, severe stroke, subarachnoid hemorrhage, post-cardiac arrest, meningitis, hepatic encephalopathy, encephalitis, or other brain infections) frequently present with an increased brain volume and reduced brain compliance. The slow increase in serum osmolality related to increased concentrations of metabolites as a result of failing kidney function will have little impact. In addition to variations in cerebral blood flow and arterial pressure, initiation of RRT will induce a rapid osmotic shift due to a drop in serum osmolality, and the extent of this shift is mostly driven by initial urea levels. The osmotic shift will then cause an increase in brain volume secondary to the osmolar gradient, with potential catastrophic consequences such as severe intracranial hypertension and brain death. According to the Monro-Kellie doctrine, the intracranial space is a fixed volume inside the skull and the cerebral pressure–volume correlation is initially linear (compensation), becoming exponential (compliance is reduced after compensatory mechanisms have reached their limits), meaning that a small increase in volume will induce a major increase in intracranial pressure (the so-called Langfitt curve).

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Therefore, patients with brain injury are at high risk of reaching the right inflection point of the curve and developing severe intracranial hypertension. Several case reports and reviews have described these complications (4, 5). Even the use of recommended “soft” RRT methods, such as sustained or continuous low-efficiency dialysis for patients with AKI and brain injury (6) will hardly moderate this shift, which occurs within the first minutes of RRT. We suggest not using the delayed RRT initiation strategy in patients at risk for elevated intracranial pressure. We believe that the best strategy for RRT modalities and initiation in this subset of patients remains to be determined. ■

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Benjamin G. Chousterman, M.D., Ph.D.*
Assistance Publique – Hôpitaux de Paris
Paris, France
Sorbonne Paris Cité
Paris, France
and
Inserm U942
Paris, France

Matthieu Jamme, M.D.
Poissy Saint Germain Hospital
Poissy, France
and
Versailles Saint-Quentin-en-Yvelines University
Villejuif, France

Nahid Tabibzadeh, M.D., Ph.D.
Assistance Publique – Hôpitaux de Paris
Paris, France
and
Sorbonne Paris Cité
Paris, France

Samuel Gaugain, M.D.
Charles Damoiseil, M.D.
Romain Barthélémy, M.D.
Assistance Publique – Hôpitaux de Paris
Paris, France

*Corresponding author (e-mail: benjamin.chousterman@aphp.fr).

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